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Syntheseses [sic] and evaluation of porphyrin derivatives for applications in medicine and in material science

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SYNTHESESES AND EVALUATION OF PORPHYRIN DERIVATIVES FOR APPLICATIONS IN MEDICINE AND IN MATERIAL SCIENCE

A Dissertation

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DEDICATION

This dissertation is dedicated to my parents in China for their unconditional love to me and my sister.

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LIST OF ABBREVIATIONS SYMBOLS

δ - chemical shift

Boc – *t*-butoxycarbonyl

br - broad

BNCT- boron neutron capture therapy

CAN - Ammonium cerium(IV) nitrate

^{13}C-NMR – carbon 13 nuclear magnetic resonance

d - doublet

DCM – dichloromethane

DDQ – 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL-H –Diisobutylaluminium hydride

DMAP – dimethylaminopyridine

EtOAc – ethyl acetate

EtOH – ethanol

^{1}H-NMR – proton nuclear magnetic resonance

HPLC – High Performance Liquid Chromatography

h – hour(s)

Hz - hertz

J - coupling constant

LET – linear energy transfer

MALDI – matrix assisted laser desorption/ionization

MeOH – methanol

min – minute(s)

MS – mass spectrometry

m/z – mass to charge ratio

OEP – octaethylporphyrin

ODCB -o-Dichlorobenzene

PDT – photodynamic therapy

ppm – parts per million

q – quartet

quint - quintet

RBF – round bottom flask

RT – room temperature

s - singlet

t – triplet

TFA – trifluoroacetic acid

TLC – thin layer chromatography

TPP – 5,10,15,20-tetraphenylporphyrin

ABSTRACT

Chapter 1 presents a concise introduction to porphyrins, especially on the synthesis of *meso*-tetraphenylporphyrins, which were synthesized during the course of my research and were used for further purposes in the following chapters.

Chapter 2 describes the synthesis of a series of cobaltacarborane-porphyrin conjugates for the boron neutron capture therapy (BNCT) of tumors. Using an efficient and high yield ring-opening reaction, *N*-substituted porphyrins were also synthesized. The spectroscopic and structural properties of these compounds are presented. These high percentage boron and amphiphilic compounds are promising boron delivery agents for BNCT (prelimary cellular studies using some of these compounds have been performed).

In Chapter 3 a new efficient route to synthesize a series of novel carboranylporphyrins is successfully developed, using Suzuki couplings on either the β or meso positions of porphyrins. Furthermore, efficient one pot syntheses of carboranylporphyrins and carboranylchlorins are reported.

Chapter 4 reports the development of a new efficient synthetic route to a series of novel carboranylpyrroles and carboranylthiophenes. Those novel monomers were found to form polymers with extremely high thermal and electrochemical stability.

Chapter 5 introduces oxacalixarene as a novel spacer to efficiently build cofacial bisporphyrins and higher oligomers. This is a general method to build a variety of cofacial architectures. The spectroscopic and structural properties of these new compounds are presented. The resulting porphyrins and their metal complexes are good models for studying energy transfer mechanisms and can also find application in the area of multi-electron redox catalysis.

Chapter 6 reports a new efficient synthetic route to carbohydrate-porphyrin conjugates.

CHAPTER 1. INTRODUCTION AND SYNTHESES OF PORPHYRINS

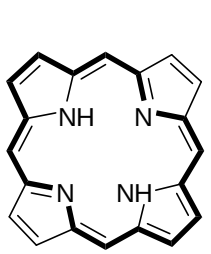
1.1. Fundamental Properties of Porphyrins

Porphyrins and related tetrapyrrolic compounds, which have been the subject of intense interest since the early 19th century, have attracted scientists from many areas due to their immense biological importance and their fascinating physical, chemical, and spectroscopic properties[1,2]. The porphyrin macrocycle (**1.1**) is an aromatic system consisting of four 'pyrrole-type' rings joined by four methine (*meso*) carbons. Although a porphyrin ring has a total of 22-π electrons, only 18 of them participate in any one of the several delocalization pathways. Due to the anisotropic effect from the porphyrin ring current, the shielded N-H protons appear at very high field (-2 to -4 ppm) in the ^{1}H-NMR spectrum, whereas the peripheral protons show up at low field (8-10 ppm) due to the presence of the deshielding environment resulting from the aromatic ring current[3]. In the visible absorption spectra, porphyrins usually show an intense Soret band[4] at around 400 nm, which results from the delocalized cyclic electronic pathway of porphyrins. Several weaker absorption bands between 450 nm and 800 nm, which are responsible for the rich color of porphyhrins, are also observed and known as Q bands.

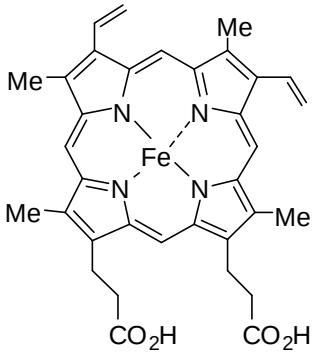
The porphyrin ring is generally stable under strongly acidic and basic conditions. Strong bases, such as alkoxides can remove the two protons (pK_a ~16) on the inner nitrogen atoms of porphyrin to form a dianion. On the other hand, the two free pyrrolenine nitrogen atoms (pK_b ~9) can be easily protonated with acids such as trifluoroacetic acid, to form a dication. The inner protons can also be replaced by a metal. Various types of metals (e.g., Zn, Cu, Ni, Sn) can be inserted into the porphyrin cavity by using various metal salts[5]. Demetalation of metalloporphyrins can usually be achieved by the treatment with acids, and different types of acids are required for the removement of different types of metals. Alkylation of the pyrrolenine

nitrogen atoms[6] can also be achieved in a similar way to protonation and metalation (see Chapter 2).

Aromatic compounds such as porphyrins used to be assumed to be planar. Although previous reported X-ray structures of simple porphyrins showed the ring to be planar, recently, there have been tremendous numbers of nonplanar porphyrins reported in the literature[7,8]. Nonplanar porphyrins have intriguing physical and biological properties due to the distortion of the porphyrin ring. Many different factors such as metalation, peripheral substitutions, alkylation of the pyrrolenine nitrogen atoms, and even protonation, can distort the nominally planar structure of the porphyrin macrocyle.



1.1



1.2

1.2. Applications of Porphyrins

As mentioned above, porphyrins and related tetrapyrrolic compounds occur widely in nature and play important roles in various biological processes. For example, heme (**1.2**), the iron(II) protoporphyrin-IX complex, is the prosthetic group in hemoglobins and myoglobins, which are responsible for oxygen transportation in red blood cells and oxygen storage in living tissue. In addition to the vital roles these compounds play in biological systems, porphyrins, especially numerous synthetic porphyrins, have also found applications outside the modeling and mimicking of natural systems. For example, they have found applications in molecular sensors,

molecular recognition, photodynamic therapy, boron neutron capture therapy, virus destruction, DNA cleavage, data storage, nonlinear optics and electrochromism. Due to their wide applications, the synthesis of porphyrins and their assemblies has become a very attractive research area[2].

Due to their selective localization in tumor cells, synthetic tetrapyrrole pigments have tremendous applications in PDT (photodynamic therapy) and BNCT (boron neutron capture therapy)[9]. PDT and BNCT are both binary cancer therapies and their side effects are limited. PDT involves the irradiation of a photosensitizer with light of a specific wavelength, which is absorbed by the photosensitizer and subsequently causes the excitation of the photosensitizer to its excited singlet state, then through intersystem crossing, to reach to its excited triplet state. The resulting excitation energy is absorbed by the triplet ground state of dioxygen (found in all living cells) and the highly toxic singlet dioxygen ($^1O_2$) is generated; this kills the tumor cells. BNCT involves the capture of thermal neutrons by boron-10 nuclei, which have been selectively delivered to tumor cells. The captured neutron releases ^{7}Li and ^{4}He nuclei with kinetic energy (~ 2.4 Mev). These two particles are extremely cytotoxic but can only travel a distance of about one cell diameter in tissues, thus it can selectively kill the tumor cell containing it (more detail in Chapter 2).

Porphyrins and metalloporphyrins are also ideal model compounds for studying light harvesting, energy and electron transfer, and multielectron redox catalysis[10]. Porphyrin-based multiporphyrin arrays and molecular wires have received much interest. In these model systems, it is important to know how individual molecules within arrays communicate with each other. So far, factors such as distance, orientation and geometry have been recognized to be important factors to control this intercommunication.

1.3. Syntheses of Porphyrins

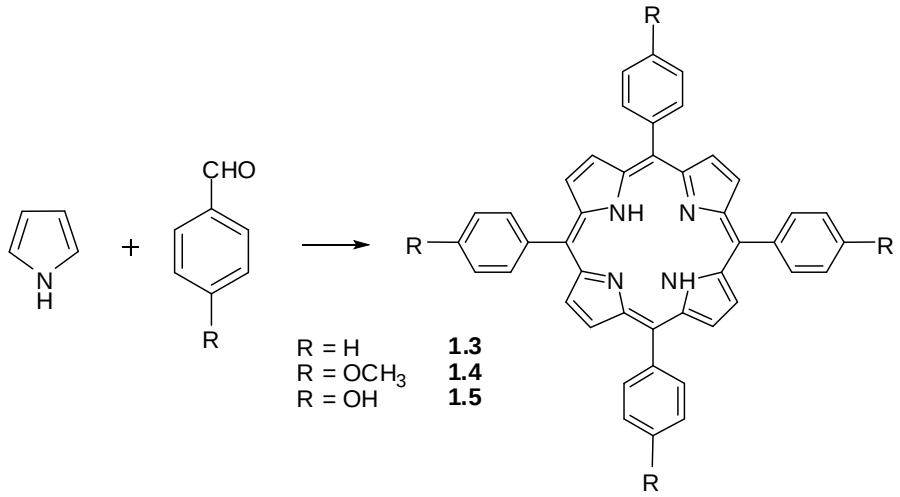
In the past 100 years, porphyrin syntheses have been developed dramatically[11]. Today, virtually any porphyrin can be synthesized from known synthetic methodology. For example, tetramerization of pyrroles, [3 + 1] condensation and [2 + 2] condensation are common methodologies[12]. Tetraarylporphyrins are synthetic porphyrins and have various applications. Here, we will focus on the syntheses of *meso*-tetraarylporphyrins. A series of symmetrical and unsymmetrical porphyrins have been synthesized and have found applications in the following Chapters in this Dissertation.

A simple way to obtain symmetrical porphyrins (such as the tetraarylporphyrins) is the acid-catalyzed condensation reaction of pyrrole with specific aldehyde, followed by oxidation of the resulting colorless porphyrinogen. This procedure, originally developed by Rothemund and Menotti[12a], has been refined by Adler and Longo[13]. It generally gives around 20% yields for tetraarylporphyrins (*Scheme 1-1*). Despite the modest yields, the relative simplicity of this method has made it well suited for preparation of large amounts of tetraarylporphyrins (i.e., >1 g of porphyrin). Later, the Lindsey group developed higher yielding and milder reaction conditions by using a Lewis acid (TFA or BF_3) as the catalyst[14]. Subsequently, Lindsey's group also developed higher concentration conditions (0.1-0.3 mol L^{-1}). Despite the slightly lower yields, this improved synthesis is more practical for larger scale preparations of tetraarylporpyrins. Also, the Lindsey method has the advantage that it can be used to prepare porphyrins that required the use of acid-unstable aldehydes not generally employed under Adler-Longo conditions.

It is possible to synthesize unsymmetrical substituted porphyrins via mixed aldehyde condensations. By using a mixture of two different aldehydes as starting materials in the Adler or Lindsey syntheses, a statistical mixture of products is obtained (*Scheme 1-2*). The desired

porphyrin is then separated by extensive chromatography (*to achieve easy separation, polarity difference of the two aldehydes are often required*). Mixed aldehyde condensation is a simple practical way to prepare unsymmetrical porphyrins. These unsymmetrical porphyrins are useful precursors for building biocojugates and porphyrin arrays. Another way to prepare this type of molecule is through direct regioselective functionalization of a symmetrical porphyrin.

1.3.1. Adler-Longo Method

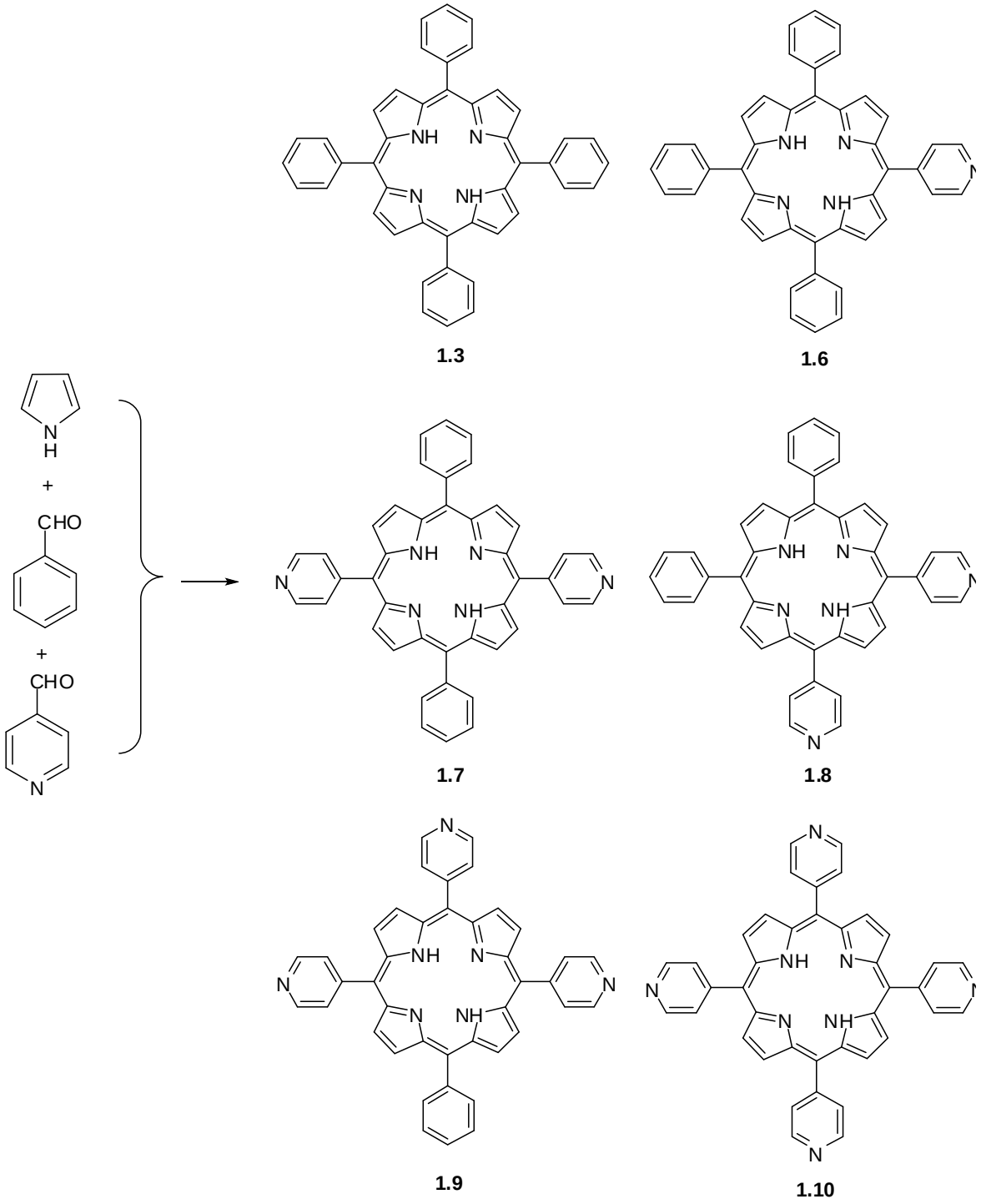


Scheme 1-1: Reaction conditions: propionic acid, reflux, air.

The simplest tetraarylporphyrin is tetraphenylporphyrin H_2TPP (**1.3**). It was obtained in 21 % yield by refluxing equivalent amount of pyrrole and benzaldehyde in propionic acid for a period of 30 minutes, under air. The target product usually contains small amount of the corresponding chlorin (dihydroporphyrin).

Similar to **1.3**, porphyrin **1.4** was also synthesized in 16 % yield on the multigram scale without the requirement of chromatographic purification (the desired porphyrin was precipitated from cold propionic acid and then filtered and washed thoroughly with methanol). Porphyrin **1.4** was then used for demethylatation reactions. Demethylation was achieved by using BBr_3 in dichloromethane (DCM), from which **1.5** was obtained in 91% yield. Compared with pyridinium

hydrochloride, which generally requires high temperatures (200-220 ℃) and gives an incompletely demethylated product, BBr_3 is found to be a powerful demethylation reagent.

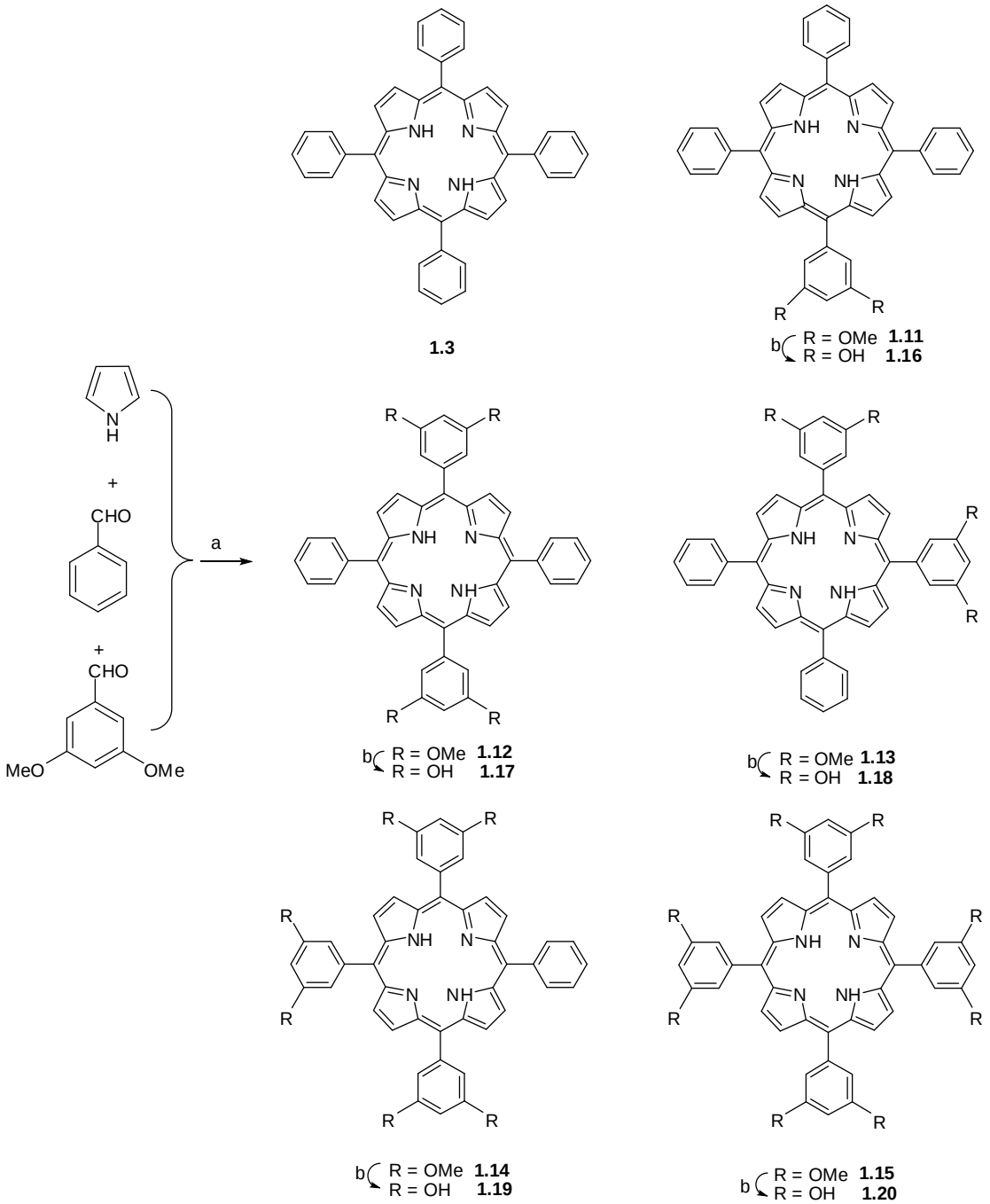


Scheme 1-2: Reaction conditions: refluxing propionic acid, air.

The Adler-Longo method is also a good choice for mixed porphyrin condensations. For example in *Scheme 1-2*, porphyrins **1.6** through **1.10** were obtained as a mixture by dropwise addition of freshly distilled pyrrole (6.25 mL) into a refluxing propionic acid (250 mL) solution of benzaldehyde (7.0 mL, 68 mmol) and pyridine-4-carboxaldehyde (3.0 mL, 31.5 mmol). The solution quickly changed color from yellow to black and refluxing was continued for a period of 1.5 hours. After the reaction was stopped, 175 mL ethylene glycol was added to the reaction mixture. The solution was stored at –20 ℃ overnight to allow the porphyrins to precipitate. The resulting porphyrins were filtered and washed repeatedly with methanol. Further column purification was performed on a silica gel column by using chloroform/ethyl acetate for elution. The order of porphyrins eluted down from the column was according to the following sequence **1.3**, **1.6**, **1.7**, **1.8**, **1.9** and then **1.10.**

Using a similar method, porphyrins **1.11** through **1.15** were also prepared. Freshly distilled pyrrole (5.6 mL, 0.08 mol) was added dropwise into a refluxing propionic acid (180 mL) solution of benzaldehyde (6.06 mL, 0.06 mol) and 3,5-dimethoxybenzaldehyde (3.55 g, 0.02 mol) The reaction mixture was refluxed for about half an hour, before cooling it down to –20 ℃ and leaving it to stand overnight. After filtration the reaction solid was washed with methanol and dried under vacuum. 1.3 g of the crude mixture of porphyrins was obtained, which was separated on silica gel column using hexane and DCM for elution to give **1.11**-**1.14**. The symmetrical porphyrin **1.15** was synthesized from 3,5-dimethoxybezaldehyde and pyrrole in 17 % yield. The yield of mixed aldehyde condensations is heavily dependent on the ratio of the aldehydes used. Depending on the desirable target compound, the ratio of aldehydes can be changed to maximize the yield of the required target porphyrin. The corresponding hydroxyphenylporphyrins (**1.16**-**1.20**) were obtained by demethylation using BBr_3 in DCM at room temperature for a period of

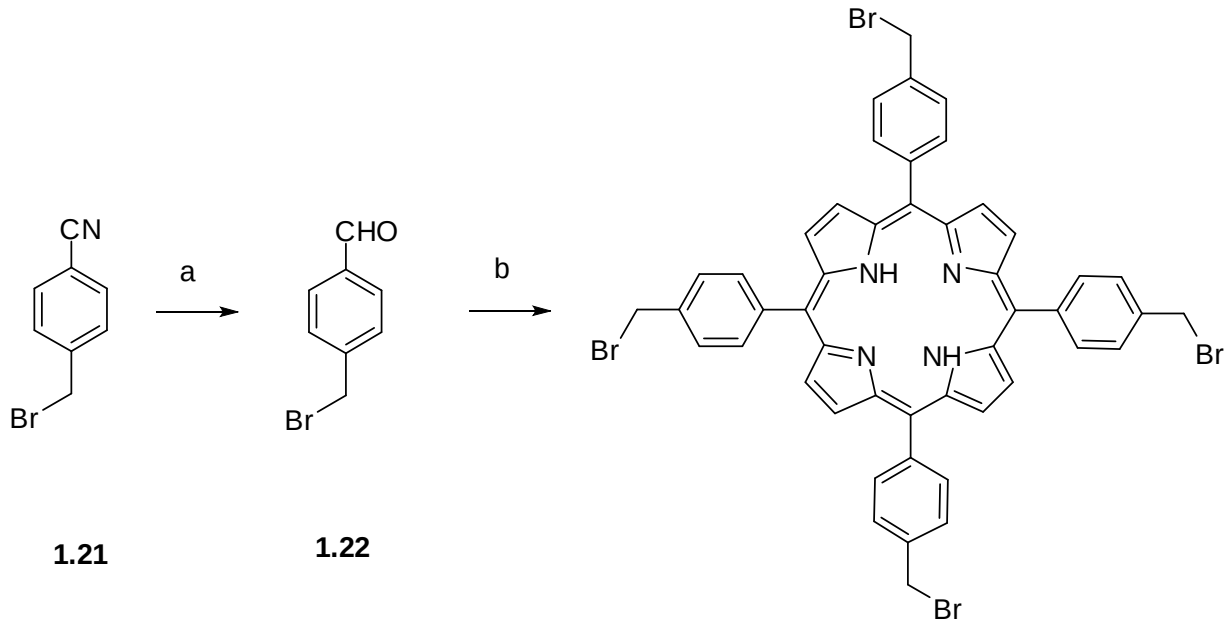
24 hours. The advantage of the Adler-Longo method is that the target porphyrin can be crystallized from the reaction mixture directly and pure porphyrin can be obtained by simply washing with water and methanol without the need for chromatography (for symmetrical porphyrins).



Scheme 1-3: Reaction conditions: (a) refluxing propionic acid, air. (b) BBr_3, DCM, r.t., 24 h.

1.3.2. Lindsey Method

However, some porphyrins can not be easily crystallized from propionic acid. In this case, the separation of porphyrins becomes troublesome. Especially for mixed aldehyde condensations, if the porphyrins can not be easily crystallized from solution, the separation is almost impossible because of the generation of many byproducts (such as expanded porphyrins, *N*-confused porphyrins, and higher oligomers) from the harsh conditions used in this reaction. Therefore the successful separation of porphyrin mixtures heavily depends on the crystallization of target porphyrins from reaction mixtures. In some cases, co-solvents, such as ethylene glycol, are added to help the crystallization of porphyrins from the reaction mixture.

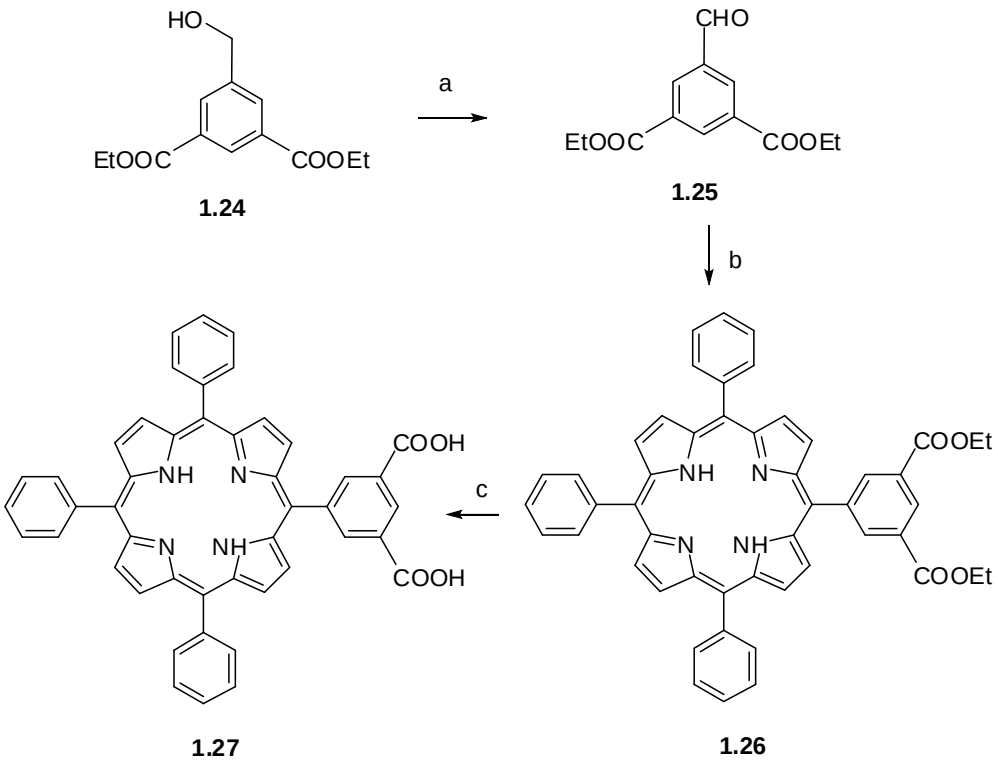


1.21 **1.22** **1.23**

Scheme 1-4: Reaction conditions: a) DIBAL-H, toluene, Argon, then H_2SO_4; b) $BF_3{\cdot}OEt_2$, DCM, r.t., then DDQ.

Meanwhile, the Lindsey method employs milder reaction conditions and generally provides higher yields of porphyrins. Besides the higher yield, there are two other main advantages that make the Lindsey method popular. Firstly, some aldehydes that are unstable under Adler

conditions can survive the milder Lindsey conditions (see *Scheme 1-4*); secondly, some porphyrins, especially those resulting from mixed aldehyde condensations which can not be crystallized and precipitated from propionic acid, can be easily purified using the Lindsey conditions because of less byproducts being generated (see *Scheme 1-5*).



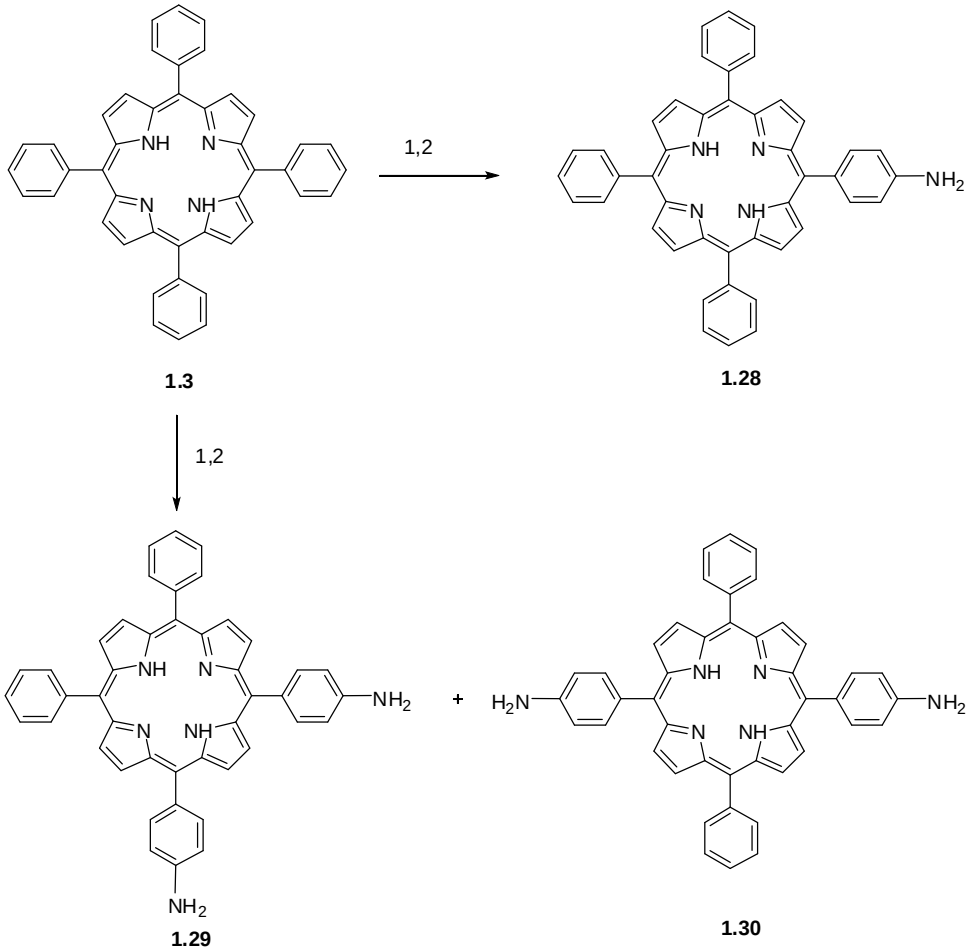
1.24 **1.25** **1.27** **1.26**

Scheme 1-5: Reaction conditions: **(**a) CAN, MeCN. (b) PhCHO, $BF_3{\cdot}Oet_2$, DCM, r.t., and then DDQ. (c) 10% NaOH (aq), THF.

As shown in *Scheme 1-4*, compound **1.21** was reduced to aldehyde **1.22** using DIBAL-H in anhydrous toluene and then quenched using H_2SO_4 solution (pH < 4 is required). This reaction gives 70-80% yield. Due to the similar polarities of **1.21** and **1.22** (this aldehyde is a little more polarer on TLC); column separation is not efficient in this case. However, recrystallization from DCM is a good method to obtain pure **1.22**. The Lindsey method was then used to make porphyrin **1.23**. By stirring equivalent amounts of **1.22** and pyrrole in distilled DCM at room temperature or even 0 ℃ in the dark for 4 hours, **1.23** was obtained in 62% yield after oxidization with DDQ and purification by passing through a pad of silica gel. The high yield of

the target porphyrin demonstrates that the Lindsey procedure is an efficient method to prepare a variety of tetraarylporphyrins, especially on the small scale. Aldehyde **1.25** was prepared in 90% yield by oxidizing the corresponding alcohol using CAN. The mixed aldehyde condensation (**1.25**/benzaldehyde = 1/4) was performed according to the Lindsey method, as described above. The resulting porphyrins are mainly H_2TPP (**1.3**) and **1.26**. Separation was performed on a silica gel column and **1.26** was obtained in 11% yield. Hydrolysis of the porphyrin **1.26** under basic condition gave porphyrin **1.27** in almost quantitative yield. Other porphyrins are also formed in this reaction but no isolation was performed for them.

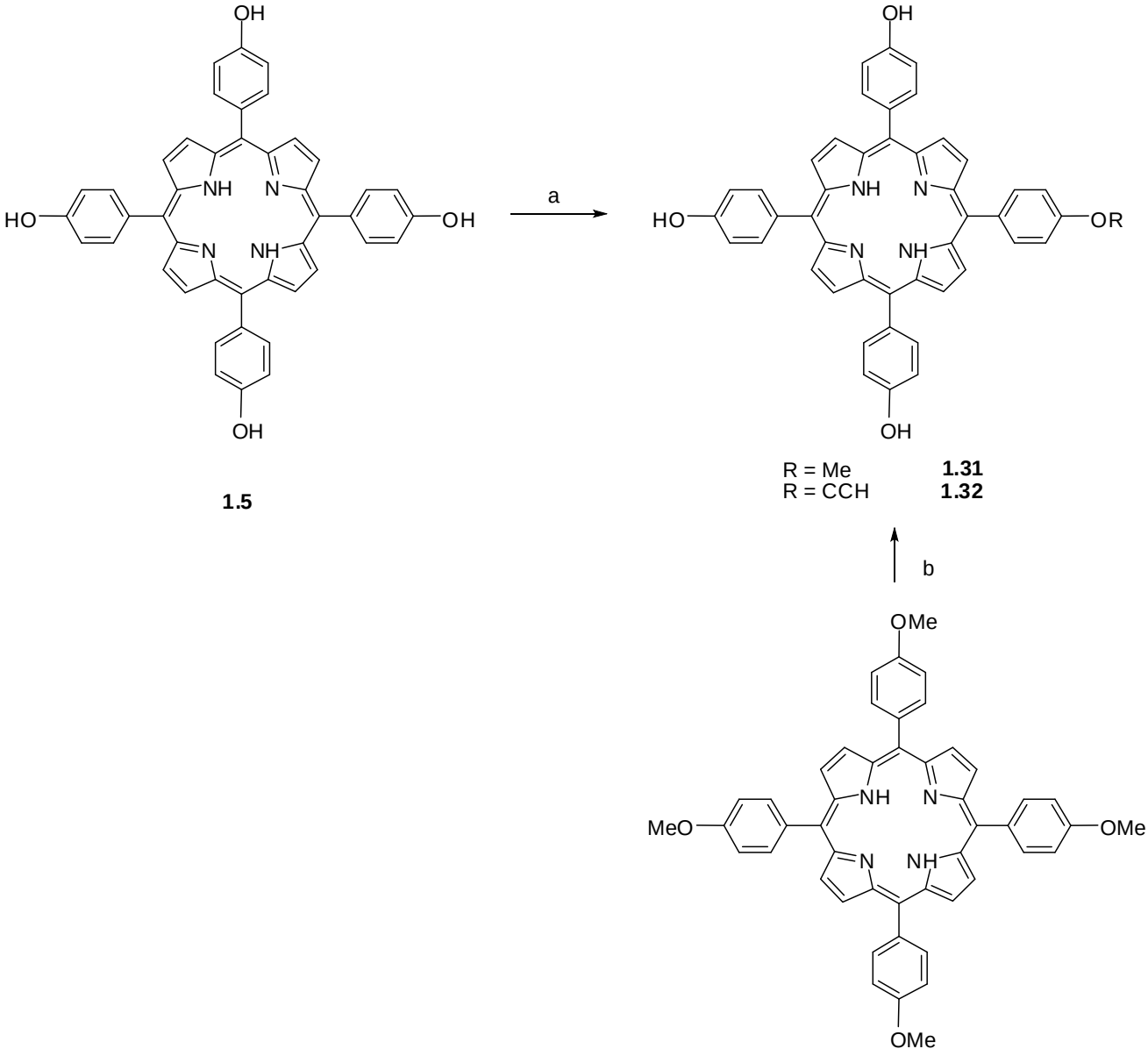
1.3.3. Asymmetrical Porphyrins from Symmetrical Porphyrins



1.3 **1.28** **1.29** **1.30**

Scheme 1-6: Reaction conditions: 1) TFA, $NaNO_2$; 2) $SnCl_2$, HCl, 65 ℃.

Besides the mixed aldehyde condensation, the selective functionalization of symmetrical porphyrins is also a good choice to prepare unsymmetrical porphyrins with desired functionality. In these cases, the mixtures can be easily separated because of the absence of other tetrapyrrole byproducts, which are often previously formed during other synthetic approaches. Two examples are given in the following paragraphs.



1.5 **1.31** **1.32**

Scheme 1-7: Reaction conditions: a) CH_3I or propargyl bromide, DMSO, K_2CO_3, 50 ℃; b) pyridium hydrochloride, 200-220 ℃.

First, H_2TPP was selectively nitrated using $NaNO_2$ in pure TFA. By controlling the amount of the $NaNO_2$ and the reaction time, **1.28** or the mixture of **1.29** and **1.30** can be obtained as the major products in these reactions[15]. Porphyrin **1.5** was mono-methylated by using 1.0-1.5 equivalent amount of CH_3I or propargyl bromide, from which porphyrins **1.31** and **1.32** were obtained. Some higher substituted porphyrins were also observed without separation. The reactions usually give 25-35% yield when performed in DMSO and K_2CO_3 was used as the base at 50 ℃. However, when these reactions were performed in acetone, when even only one equivalent amount of CH_3I or propargyl bromide was provided, more highly substituted porphyrins were preferentially formed rather than the mono-substituted porphyrins. Porphyrin **1.31** was also obtained from incomplete demethylation of **1.4** by using pyridium hydrochloride at high temperature.

1.4. Conclusions

In summary, the fundamental properties and applications of porphyrins and related compounds have been discussed. The methodology for porphyrin syntheses were presented, from which more than 26 *meso*-tetraphenylporphyrins were synthesized in the present work. These porphyrins are further used in the following Chapters of this Dissertation as important starting materials. Some porphyrins (**1.16**-**1.20**) are interesting compounds for studying structure/activity relationships for applications in PDT**.**

1.5. Experimental

Mixed porphyrin condensation: 5-(3,5-Dimethoxyphenyl)-10,15,20-triphenyl porphyrin, 5,15-di(3,5-dimethoxyphenyl)-10,20-diphenylporphyrin, 5,10-di(3,5-dimethoxyphenyl)-15,20-diphenylporphyrin, 5-phenyl-10,15,20-tri(3,5-dimethoxyphenyl)porphyrin were synthesized by mixing benzaldehyde and 3,5-dimethoxybenzaldehyde with pyrrole in refluxing propionic acid.

The reaction mixture was placed into a refrigerator at –20 ℃ overnight and the porphyrin precipitate was filtered and washed with methanol. The mixed porphyrin residue was subjected to flash column chromatography on silica gel with CH_2Cl_2 as eluent, where 5-(3,5-dimethoxyphenyl)-10,15,20-triphenylporphyrin (**1.11**), 5,15-di(3,5-dimethoxyphenyl)-10,20-diphenylporphyrin (**1.12**), 5,10-di(3,5-dimethoxyphenyl)-15,20-diphenylporphyrin (**1.13**), and 5-phenyl-10,15,20-tri(3,5-dimethoxyphenyl)porphyrin (**1.14**) were isolated as the second, third, fourth, and fifth fractions, respectively. 5-(3,5-Hydroxyphenyl)-10,15,20-triphenylporphyrin (**1.16**) was prepared from the corresponding 5-(3,5-dimethoxyphenyl)-10,15,20-triphenylporphyrin according to a literature procedure.

Synthesis of 5,15-di(3, 5-hydroxyphenyl)-10,20-diphenylporphyrin (1.17): To a dry CH_2Cl_2 solution (150 mL) of 5,15-di(3,5-dimethoxyphenyl)-10,20-diphenylporphyrin (0.56 g, 0.76 mmol) at –20 ℃ was added dropwise a CH_2Cl_2 solution (5 mL) of BBr_3 (2.5 mL, 0.026 mol) with vigorous stirring under argon over a period of 30 min. The reaction mixture was then stirred for 24 h at room temperature. The mixture was poured into water and was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with successively with brine and aqueous $NaHCO_3$ solution. The organic solution was then dried over Na_2SO_4 and evaporated to dryness, giving the title porphyrin 462 mg (0.68 mmol) as purple crystals in 89.4% yield. MALDI-TOF-MS for $C_{44}H_{30}N_4O_4$: m/z Calcd, 679.234 $[M+H]^+$, found 679.076. ^{1}H-NMR (acetone-d_6): 9.04 (d, 4H, β-H), 8.85 (d, 4H, β-H), 8.70 (s, 4H, OH), 8.25 (m, 4H, o-phenyl-H), 7.83 (m, 6H, m, p-phenyl-H), 7.25 (d, 4H, o-Ar-H), 6.83 (t, 2H, p-Ar-H), -2.77 (s, 2H, NH).

Synthesis of 5,10-di(3, 5-hydroxyphenyl)-15,20-diphenylporphyrin (1.18): To a dry CH_2Cl_2 solution (20 mL) of 5,10-di(3,5-dimethoxyphenyl)-15,20-diphenylporphyrin (92 mg, 0.125 mmol) at –20 ℃ was added dropwise a CH_2Cl_2 solution (1 mL) of BBr_3 (0.43 mL, 4.5 mmol)

with vigorous stirring under argon over a period of 5 min. The reaction mixture was then treated as described above, giving the target porphyrin 78 mg (0.115 mmol) as purple crystals in 91.9% yield. MALDI-TOF-MS for $C_{44}H_{30}N_4O_4$: m/z calcd, 679.234 $[M+H]^+$, found 679.148. ^{1}H-NMR (acetone-d_6): 9.05 (d, 4H, β-H), 8.84 (m, 4H, β-H), 8.71 (s, 4H, OH), 8.22 (m, 4H, o-phenyl-H), 7.80 (m, 6H, m, p-phenyl-H), 7.27 (d, 4H, o-Ar-H), 6.85 (d, 2H, p-Ar-H), -2.76 (s, 2H, NH).

Synthesis of 5-phenyl-10,15,20-tri(3,5-dihydroxyphenyl)porphyrin (1.19): To a dry CH_2Cl_2 solution (20 mL) of 5-phenyl-10,15,20-tri(3,5-dimethoxyphenyl)porphyrin (79.2 mg, 0.10 mmol) at –20 ℃ was added dropwise a CH_2Cl_2 solution (1 mL) of BBr_3 (0.52 mL, 5.5 mmol) with vigorous stirring under argon over a period of 5 min. The mixture was then treated as described above, giving target porphyrin 64 mg (0.115 mmol) as purple crystals in 90.5% yield. MALDI-TOF-MS for $C_{44}H_{30}N_4O_6$: m/z calcd, 711.224 $[M+H]^+$, found 711.222. ^{1}H-NMR (acetone-d_6): ^{1}H-NMR (acetone-d_6): 9.04 (d, 6H, β-H), 8.84 (d, 2H, β-H), 8.70 (s, 6H, OH), 8.24 (m, 2H, o-phenyl-H), 7.83 (m, 3H, m, p-phenyl-H), 7.25 (t, 6H, o-Ar-H), 6.84 (m, 3H, p-Ar-H), -2.76 (s, 2H, NH).

Synthesis of 5-(4-methoxyphenyl)-10,15,20-tri(4-hydroxyphenyl)porphyrin 1.31: Tetra(4-hydroxyphenyl)porphyrin (170.0 mg, 0.25 mmol) and K_2CO_3 (280.0 mg, 2 mmol) were heated (60 ℃ oil bath) in 40 mL DMSO in a 100 mL round botton flask under argon for 15 minutes. Then iodomethane (0.016 mL, 0.26 mmol) was added to the solution and the mixture was stirred overnight. The reaction mixture was poured into 200 mL brine and extracted with ethyl acetate until colorless. Evaporation of the mixture gave a residue rthat was separated using a silica gel column eluted with chloroform and ethyl acetate. The target compound then was recrystallized from ethyl acetate and hexane and dried under vacuum, giving 42.6 mg (24.8%, 0.062 mmol).

HRMALDI-TOF-MS for $C_{45}H_{32}N_4O_4$: calcd, 693.2501$[M+H]^+$, found 693.2468. ^{1}H-NMR spectrum was identical with that in the literature.[16]

1.6. References

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CHAPTER 2: PORPHYRIN-COBALTACARBORANE CONJUGATES FOR BORON NEUTRON CAPTURE THERAPY

2.1. Introduction

Boron-containing compounds have been widely studied for boron neutron capture therapy (BNCT) of cancer[1]. BNCT is a binary radiation therapy modality that brings together two components that, when kept separated from each other, have only minor effects on cells. The first component is a stable isotope of boron (boron-10) that can be concentrated in tumor cells by attaching it to tumor-seeking compounds. The second is a beam of low-energy neutrons. Boron-10 in or adjacent to the tumor cells disintegrates after capturing a neutron and the highly energetic heavily charged particles produced (*Equation 2-1*) destroy only those cells in close proximity to it; these are primarily cancer cells and adjacent normal cells are left largely intact. Despite the fact that it is under promising clinical trials and many significant achievements have been made in the development of boron-containing BNCT agents, the slow evolution of effective drug-targeting methodologies for the selective delivery of sufficient amounts of boron to cancer cells remains as an important obstacle to the wide applications of these compounds in BNCT treatment of cancers.

$$^{10}B + {}^{1}n \longrightarrow {}^{4}He^{2+} + {}^{7}Li^{3+} + \gamma + 2.4MeV$$

Equation 2-1: The boron neutron capture reaction

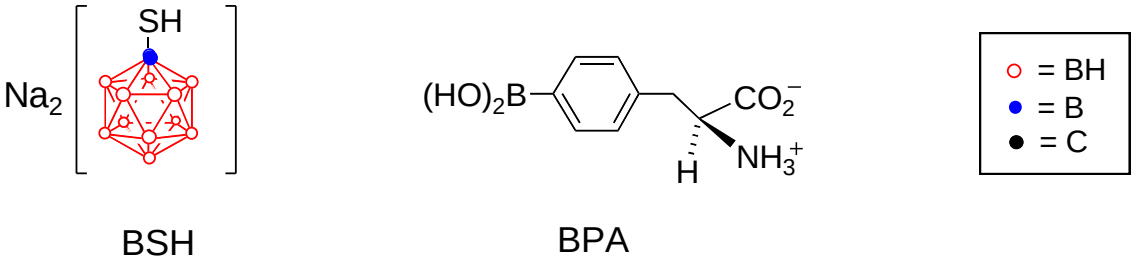


Figure 2-1: BNCT reagents currently in clinical trials.

Figure 2-1 shows two BNCT reagents that are under clinical trials. However, these 1st generation BNCT reagents can not selectively localize and be retained in tumors. In case of BPA, the boron content is very low. Early clinical BNCT experiments failed mainly due to the inadequate concentration of ^{10}B in the tumor tissue and/or the lack of selective distribution of ^{10}B[1]. During radiation, the latter leads to the damage to normal tissue. Thus, one of the biggest challenges for chemists in BNCT is the development of water-soluble, high-boron containing compounds that can be selective uptaken or retained by tumors. Many different substituted boron clusters, mainly closo-$B_{12}H_{12}^{2-}$, closo-$B_{10}H_{10}^{2-}$ and the three isomeric dicarbo-closo-dodecaborane species, were synthesized because of their high boron percentage[1]. Recently, the conjugation of multiple boron clusters with biological macromolecules and the synthesis of various dendrimers containing boron clusters have attracted much interest[2] as part of efforts to achieve even higher cellular ^{10}B concentrations. More recently, metallacarboranes, especially cobaltabisdicarbollide anion $[Co(C_2B_9H_{11})_2]^-$ have received much interest[3] as BNCT agents because of their remarkable stability to acid, and moderate base, and toward high temperature and intense radiation, as well as their high boron content and their low toxity (LD_{50} = 0.08750 mg/kg)[4,5]. More importantly, successful synthesis of the zwitterionic [3,3'-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)] has opened up an efficient way to synthesize new mono-substituted cobaltacarborane complexes[6,7].

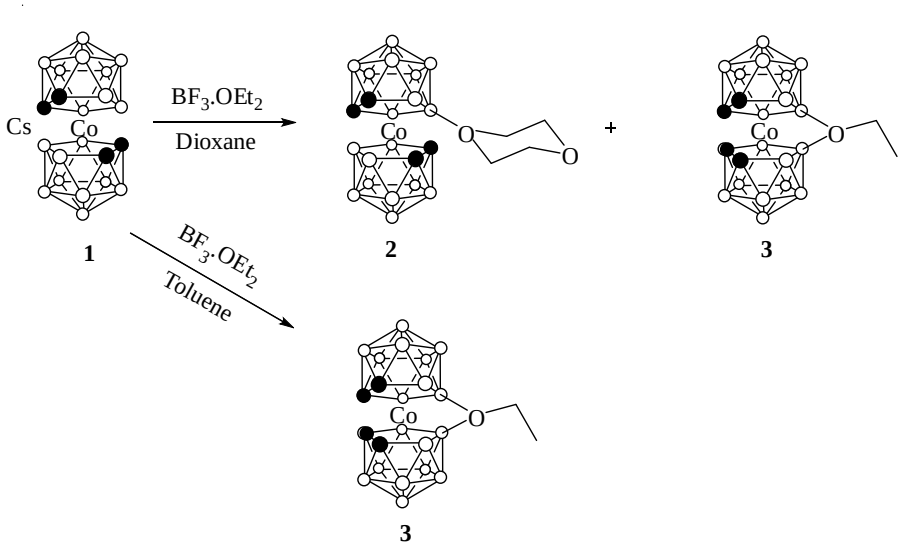
In order to achieve high tumor selectivity, various carriers, such as porphyrins, monoclonal antibodies, epidermal growth actors, nucleosides, amino acids, and liposomes, have been used to selectively deliver boron clusters to the tumor cells[1]. Among these, porphyrins are very promising, not only because of their high selective uptake but also because of their persistence within tumors[1c] and low dark cytoxities (as demionstrated in PDT). However, the number and

types of boronated porphyrin compounds are still limited[1c,8,9] because of lengthy synthetic routes and low overall reaction yields. There also exists a lack of structure/activity relationship studies for these types of compounds, which would allow the further design of promising BNCT candidates. Meanwhile, the structural modification and conformational distortion of porphyrins are widely studied because of the potential application of these factors to control the properties and functions of diverse tetrapyrroles in biological systems. Porphyrins with substitutents at a pyrrolenic nitrogen atom, the so-called "*N*-substituted porphyrins", are well-known for causing conformational distortion of the porphyrin planar structure through the sp^3 hybridization of one of the pyrrolenic nitrogens[10]. In other words, the *N*-substituent groups force the macrocycle to be nonplanar. *N*-Substituted porphyrins, were first synthesized as laboratory curiosities, and have revealed significant biochemical and biomedical properties since around twenty year's ago[11]. These compounds are powerful inhibitors of the enzyme ferrochelatase, which is essential for the formation of heme for hemoglobin, myoglobin and cytochromes, and is produced in a biochemical mono-oxygenation process catalyzed by cytochrome P-450 enzymes. Besides the important role they have played in understanding biological processes, these synthetic novelty *N*-substituted porphyrins also have potential applications in catalysts[12a], molecular recognition[12b,c], medicine[12d] and energy transfer[12e]. Novel macrocycles from *N*-substituted porphyrins and analogs by ring expansion or reduction are often reported[13]. Despite the potentially wide applications of these compounds, the synthetic approaches to *N*-substituted porphyrins are very limited; harsh reaction conditions are often involved and low yields are generally provided.

In this chapter, development of an efficient method to conjugate porphyrins with cobaltacarboranes through ring opening reactions is reported. More than twenty novel boronated

porphyrins were synthesized and fully characterized by NMR, HRMS, HPLC, UV-vis and fluorescence. Cellular studies of some of these compounds were also performed.

2.2. Reinvestigated Synthesis of Compound 2



Scheme 2-1: Compounds **2** and **3** Syntheses.

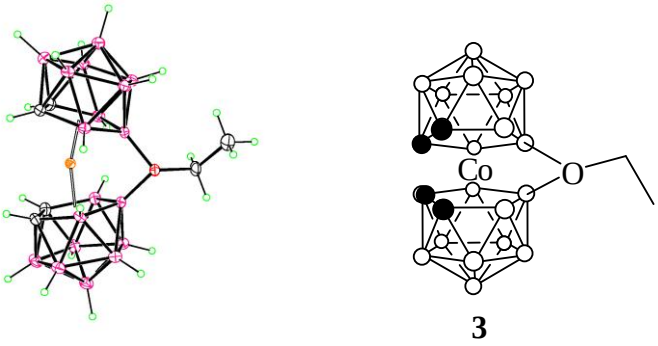


Figure 2-2: Molecular structure of **3**: X-ray structure, left; chemical structure, right.

Metallacarboranes were first reported in 1965 and belong to the large family of metallocene-type complexes. Among these, compound **1,** the cobaltabisdicarbollide anion [3,3'-Co(1,2-$C_2B_9H_{11})_2]^-$, was among the first to be synthesized, and has been extensively investigated[14]. The synthesis of compound **2** was first reported in 1997[6a] and then modified by Teixidor, et al.[6b]. However, when following the modified method (refluxing compound **1** with BF_3-Et_2O in dioxane), not only the target compound **2** was formed, but also a minor fraction **3** (4% yield) was

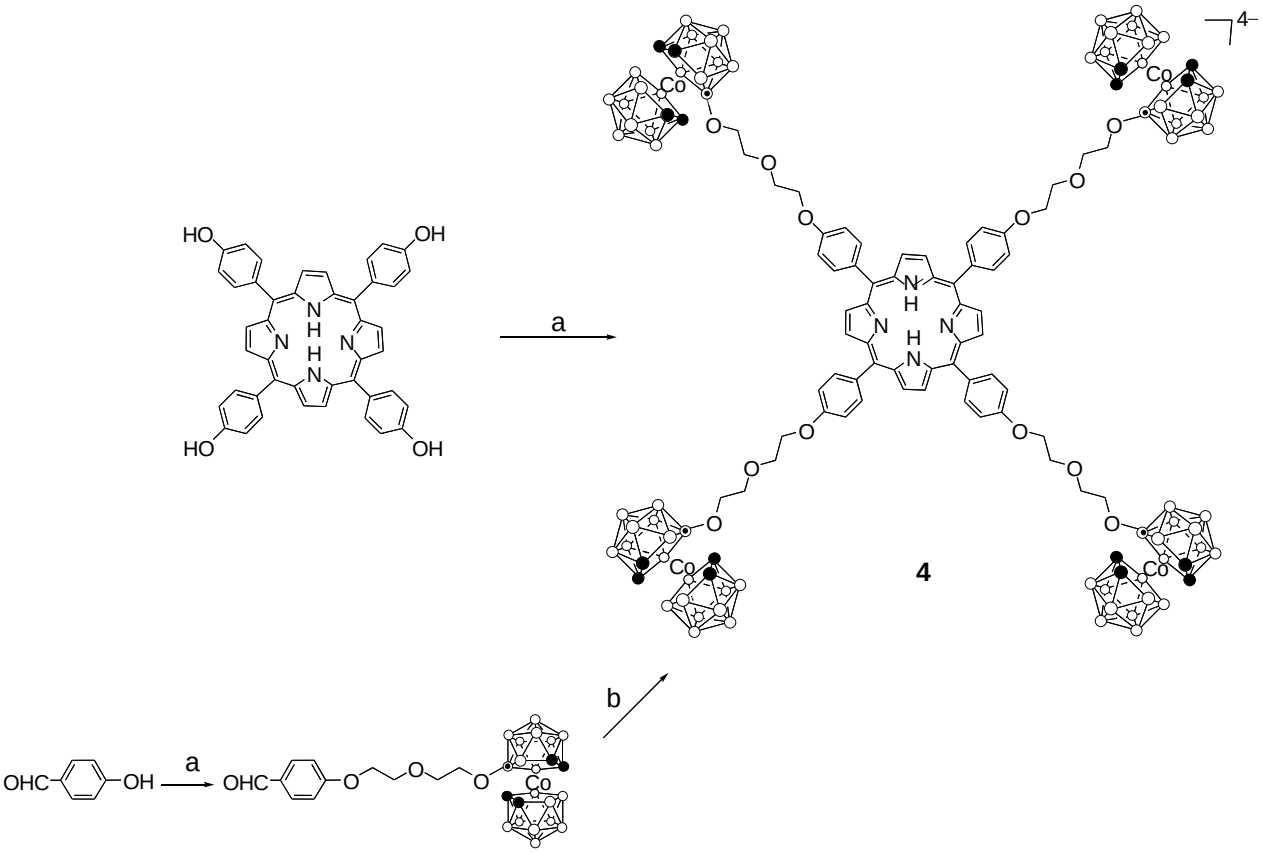
obtained, which is slightly less polar than **2**. These two compounds were separated by flash column chromatography using a mixture solvent of DCM/hexane. The X-ray structure of **3** is shown in *Figure 2-2*, in which there is a bridged oxonium [8,8'-μ-(C_2H_5O)-3,3'-Co(1,2-$C_2B_9H_{10})_2$], previously synthesized in a very low yield (5%)[6c] from heating **1** in acetic anhydride in the presence of sulfuric acid. The structure of **3** is similar to the known methyloxonium derivative [8,8'-μ-(CH_3O)-3,3'-Co(1,2-$C_2B_9H_{10})_2$][6d]. The C_2B_9 pentagonal planes bound to the cobalt atom are non-parallel due to the short oxygen bridge (B–O = 1.5 Å, B(8)–O–B(8') = 92). The dihedral angle defined by those planes was 28 °.

In order to improve the yield of **3**, compound **1** was refluxed with $BF_3{\cdot}Et_2O$ in toluene. In this case, **2.3** was isolated in 20% yield. This result indicated that the formation of **3** was from the reaction between **1** and diethyl ether. In fact, this is a better method to synthesize the boron-bridged oxonium derivative of **1**.

2.3. Porphyrin-Cobaltacarborane Conjugates from Phenol Containing Porphyrins

Compound **2** is a very valuable precursor for further functionalizations due to the presence of the six-member ring, which can be easily opened by nucleophilic reagents under mild conditions. Two commercially available porphyrins, tetrakis(4-hydoxyphenyl)porphyrin and tetrakis(3,5-dihydroxyphenyl)porphyrin were first selected as the nucleophilic species to react with **2** for two reasons: firstly, the highly nucleophilic character of the phenolate group resulting from deprotonation by an inorganic base would provide sufficient nucleophilicity to open the exo-cluster aliphatic ring of **2**; secondly, the resulting compounds **4** and **10** are highly boronated compounds and have good water-solubility. As shown in *Scheme 2-2*, tetrakis(4-hydoxyphenyl)porphyrin and tetrakis(3,5-dihydroxyphenyl)porphyrin reacted with excess

amount of **2** in the presence of potassium carbonate provided excellent yields of the desired porphyrins **4** and **10.**



Scheme 2-2: Lindsey's method was used for synthesis of compound **4.** Reaction conditions: a) acetone, compound **2**, K_2CO_3; b) DCM, $BF_3.OEt_2$, then DDQ.

The reactions normally took 3 days to finish for **10** as monitored by reversed phase HPLC. Excess amounts of **2** were used to drive the reaction to completion. When the reaction was monitored using MALDI mass spectrometry, it seemed that potassium carbonate also can react with **2** at 60 ℃ in acetone. However, the reaction was still very efficient when **2** was added in several portions. Due to the low solubility of **4** and **10** in ethyl ether, after washing with water and extracting with ethyl acetate, the reaction residues were further washed with diethyl ether to get rid of excess **2** (in some cases, some byproducts resulting from the reaction could also be

washed away with diethyl ether). Thus, pure products were easily obtained in this reaction in high yields without the need for chromatographic separation.

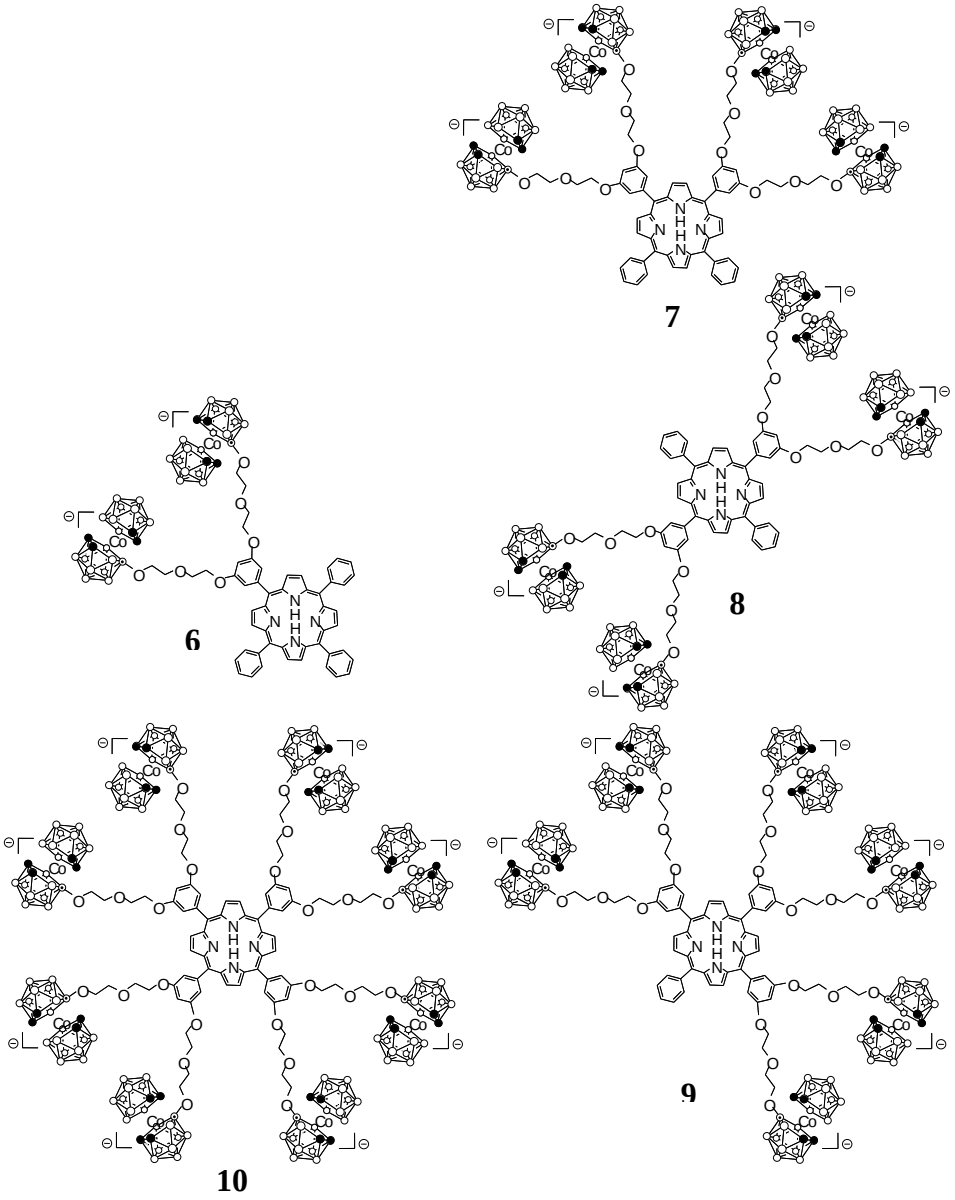


Figure 2-2: Structures for compounds **6-10.**

On the other hand, the target porphyrin **4** could also be prepared via the Lindsey method[14] (*Scheme 2-2*). The key aldehyde **5** was synthesized from 4-hydroxybenealdehyde and compound **2** using the inorganic base, potassium carbonate, in acetone. After passing through a pad of silica

gel to remove excess aldehydes (using ethyl acetate as eluting solvent), compound **5** was isolated in 97% yield. Aldehydes and pyrrole condensation reaction was performed in the mixture of 90% DCM and 10% tetrahydrofuran with $BF_3.Et_2O$ as catalyst, from which porphyrins **4** afforded in 20% yield. However, compared to the first method, this method was much less efficient.

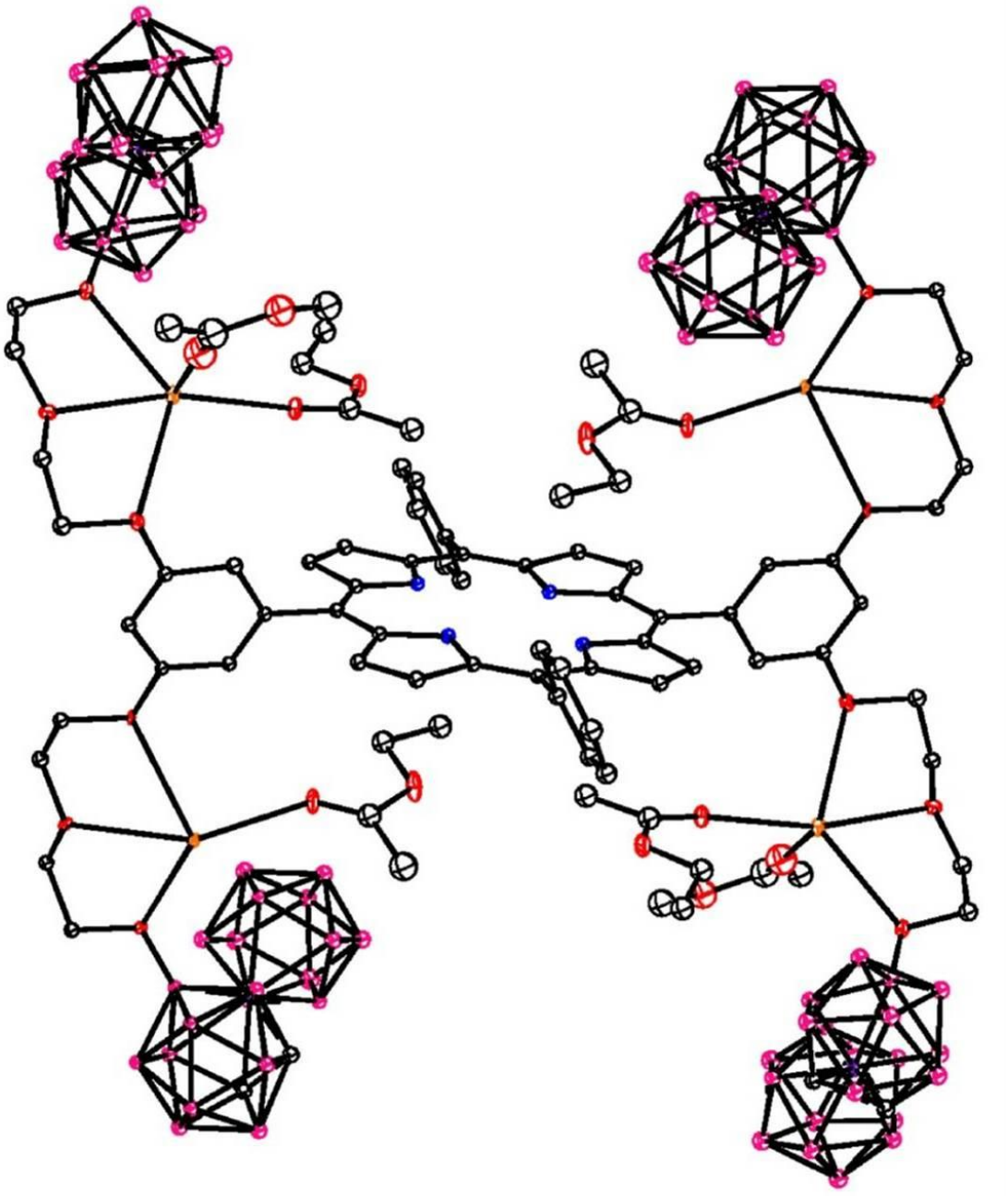


Figure 2-3: X-Ray structure of compound **8.**

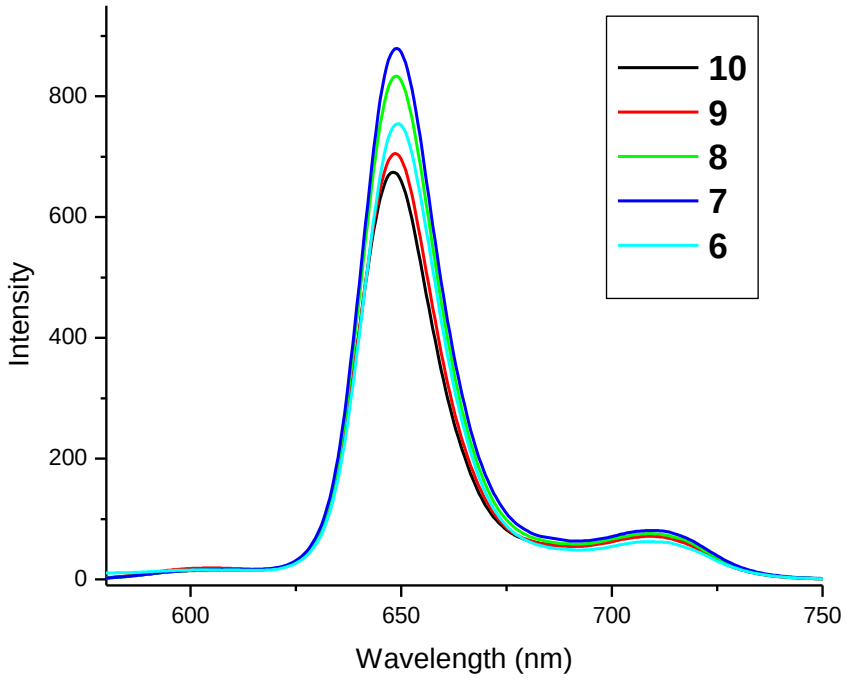


Figure 2-4: Fluorescence spectra of **6-10** in acetone at 1×10^{-6} M. Exited at 412 nm.

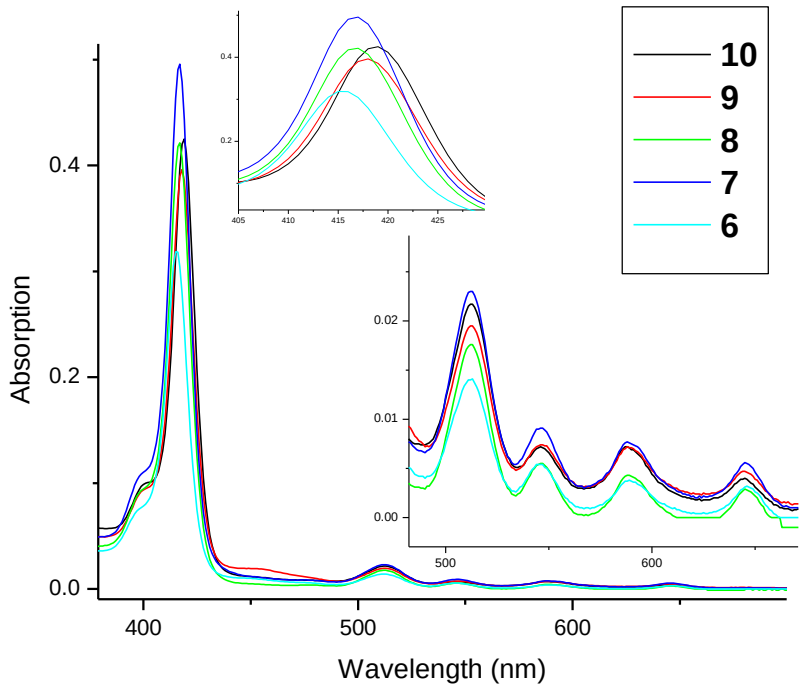


Figure 2-5: UV-vis spectra of **6-10** in acetone at 1×10^{-6} M.

In order to study structure/activity relationships, a series of porphyrins were synthesized by mixing 3,5-dimethoxybenzaldehyde and benzaldehyde using an Adler-Longo mixed condensation in boiling propionic acid (see Chapter 1). The mixed porphyrins were separated by silica gel column chromatography and then demethylated using BBr_3 in DCM. Then, porphyrins **6**-**9** (*Figure 2-2*) were synthesized in high yields by using the same method as for **4** and **10**. The decreased yield for **6** was attributed to its significant solubility in ether. A higher yield was obtained when column chromatography was used and a mixture of ethyl acetate and acetone was used for elution.

Table 2-1. Spectral Properties of Porphyrin-Cobaltacarboranes at Room Temperature.

Porphyrin	A in DMSO λmax (nm)[a]	A in HEPES buffer λmax (nm)[b]	Emission[c] λmax (nm)	Φ_f[d] in DMSO
6	313, 420, 514, 551, 590, 647	312, 421, 518, 554, 595, 651	608, 652, 708	0.20
7	314, 421, 514, 550, 591, 648	316, 425, 517, 557, 594, 648	608, 651, 708	0.19
8	314, 421, 514, 551, 590, 646	316, 425, 517, 557, 601, 649	608, 651, 708	0.21
9	314, 422, 514, 550, 590, 647	313, 426, 517, 558, 594, 644	608, 651, 708	0.20
10	315, 424, 515, 554, 590, 644	312, 429, 517, 557, 594, 644	607, 650, 708	0.21

[a] 1×10^{-6} M solution in DMSO [b] 1×10^{-6} M solution in 20 mM HEPES buffer containing 1% DMSO; [c] excitation at 420 nm; [d] calculated using 5,10,15,20-tetraphenylporphyrin as the standard.

All of the conjugates were characterized by HRMS, NMR, UV-Vis and HPLC, and in the case of **8**, by X-ray crystallography. A single crystal of porphyrin **8** was obtained by recrystallization from ethyl acetate/hexane. The crystal contains two independent molecules lying on inversion centers, only one of which is illustrated in *Figure 2-3*. The porphyrin core is

essentially planar, with a mean deviation of 0.025 Å for its 24 atoms. The unsubstituted phenyl group forms a dihedral angle of 64.9(2)˚ with the porphyrin plane, and the substituted phenyl group a 79.3(3)˚ angle with the porphyrin. The Co atoms are coordinated in parallel sandwich fashion by the carborane ligands. Co-B,C distances are in the range 1.969(10)-2.149(9)Å, with average Co-C distance 2.030 Å and average Co-B distance 2.095 Å. The K^+ cations are coordinated by ethereal O atoms of the side chains, as well as by ethyl acetate solvent molecules.

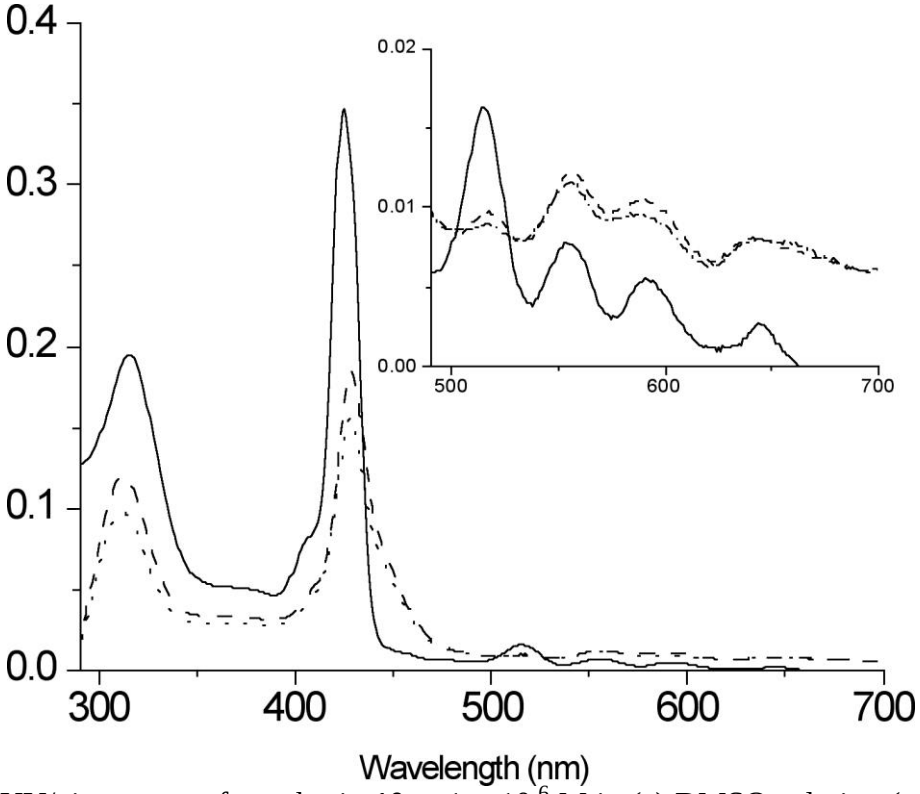


Figure 2-6: UV/vis spectra of porphyrin **10** at 1×10^{-6} M in (a) DMSO solution (solid line), (b) freshly prepared HEPES buffer (20 mM, pH = 7.4) containing 1 % DMSO (dash line), and (c) solution b after 24 h. The inset shows amplification of the Q band region.

All conjugates are highly soluble in polar solvents, such as in methanol, acetonitrile, acetone, ethyl acetate, DMF, and DMSO, but are poorly soluble in water. The above conjugates have similar UV-vis (*Figure 2-5*) and fluorescence (*Figure 2-4*) spectra to their mother compounds, giving a Soret band at around 420 nm and emission around 650 nm with 0.2 fluorescence quantum yields (*Table 2-1*). Interestingly, the Soret bands have a 1-2 nm red shift with

increasing number of cobaltacarborane cages. However, in HEPES buffer (20 mM, pH 7.4) containing 1% DMSO (prepared by dilution of a DMSO stock solution into HEPES buffer), all conjugates showed red-shifted (1-3 nm) and broadened absorption bands compared with the DMSO solutions, as well as fluorescence quenching, indicating aggregation.

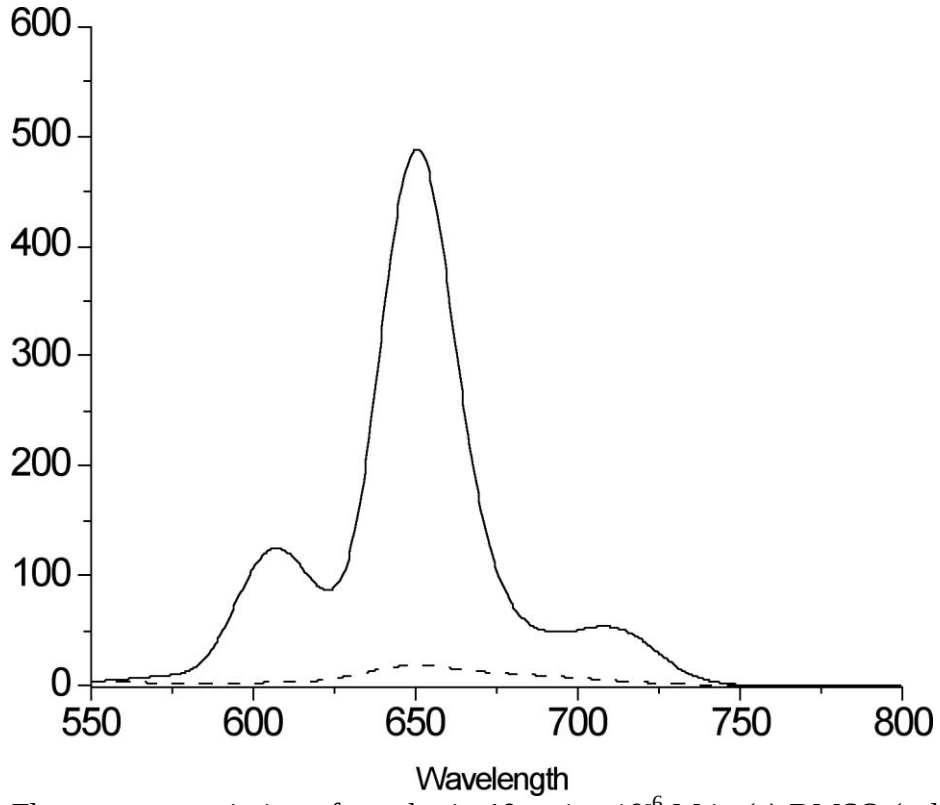
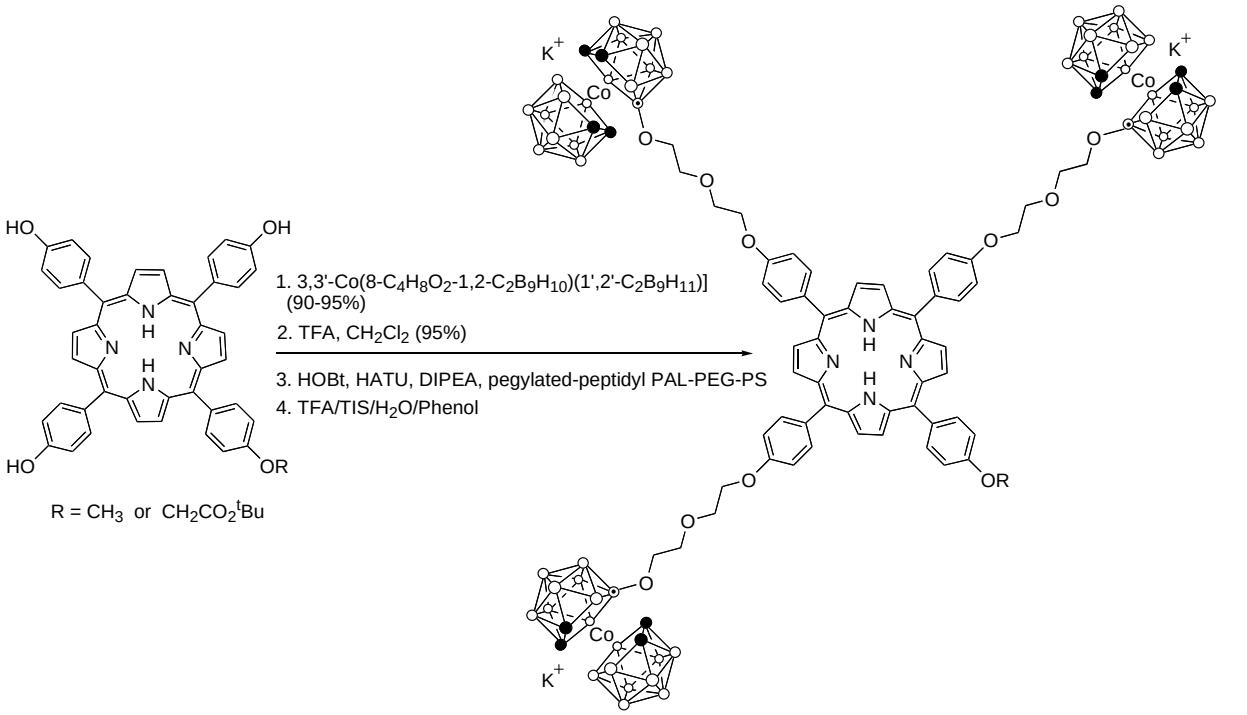


Figure 2-7: Fluorescence emission of porphyrin **10** at 1×10^{-6} M in (a) DMSO (solid line), and (b) freshly prepared HEPES buffer (20 mM, pH = 7.4) containing 1 % DMSO (dash line). Excitation was at 420 nm.

The aggregation behavior of the cobaltabisdicarbollide anion[16] and of a porphyrin-cobaltacarborane conjugate[17] in aqueous solutions have recently been investigated. In agreement with these studies, we observed a remarkable decrease in the intensity of the Soret band and a red-shifted broadened band in the absorption spectra of all conjugates in HEPES buffer. A dramatic quenching of the porphyrin fluorescence was also observed. For example the fluorescence of porphyrin-cobaltacarborane conjugate **10** in HEPES buffer was less than 1% of that in DMSO solution (*Figure 2-7*). Furthermore, the aggregation was time-dependent; after 24

hours the absorption spectra of conjugate **10** in HEPES buffer showed a further decrease in the Soret band intensity and a 1 nm red-shift. Interestingly, the aggregation phenomenon is easily diagnosed since it is often accompanied by a color change, from red (in DMSO) to green (in HEPES buffer, 20 mM, pH 7.4), even in much diluted (ca. 10^{-4} M) solutions. The green transparent solutions slowly became cloudy with standing (in about 2-4 weeks), and upon sonication once again became transparent.



Scheme 2-3: Synthesis of porphyrin-cobaltacarborane-HIV-I Tat.

All conjugates behaved similarly, in agreement with previous studies using mono- and tetra-cobaltacarborane-substituted porphyrins. The average particle size of the aggregates was determined by dynamic light scattering (DLS) and the particle sizes range from 10 nm to 2 μm, even in freshly prepared solutions filtered through a 200 nm filter. These results indicate that these conjugates aggregate in HEPES buffer and rapidly undergo secondary aggregation. The

secondary aggregated particles likely break down the primary aggregates upon filtration or sonication. The conjugate aggregates were visualized by AFM by collaboration with Dr. Garno's group (data not shown).

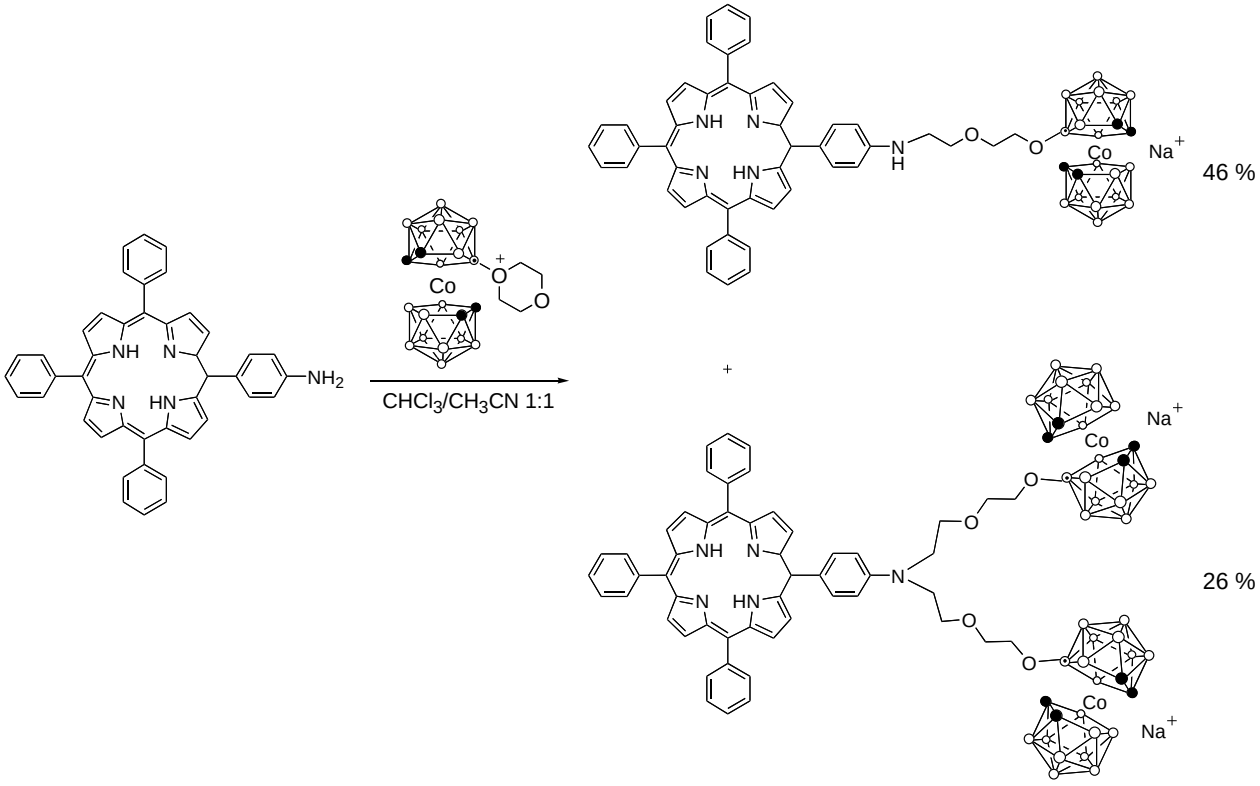
Due to the high efficiency of this reaction, we decide to synthesize the 2nd generation of these compounds by conjugating cell-targeting peptides to the porphyrin-cobatacarborane conjugates to achieve better cell localization properties for these compounds. A cell-penetrating peptide sequence, such as that found in the human immunodeficiency virus I transcriptional activator (HIV-1 Tat)[18] was selected because our group has recently reported that it efficiency delivers a non-boronated porphyrin intracellularly[19].

By monoalkylation of tetra(4-hydroxyphenyl)porphyrin, the hydroxyporphyrins with alkyne, methyl or carboxylic acid (t-Bu protected) groups were prepared in 20-30% yield. The nucleophilic ring-opening reaction of the dioxane ring of cobaltacarborane **2** using hydroxyarylporphyrins afforded the corresponding porphyrin-cobaltacarborane conjugates **11** and **12a** in 91 and 93% yield, respectively. The free carboxylic acid group of compound **12** was converted into the corresponding hydroxybenzotriazole ester and coupled to a pegylated-peptide-PAL-PEG-PS resin containing the HIV-1 Tat 48-60 sequence (in collaboration with Dr. Sibrian-Vazquez). After cleavage and deprotection from the solid support using 88:2:5:5 TFA/TIS/phenol/H_2O, the porphyrin-peptide-cobaltacarborane conjugate **13** was isolated by reversed-phase HPLC in 8% yield.

2.4. Porphyrin-Cobaltacarborane Conjugates from Amine Containing Porphyrins

Next, we turned to use a weaker amine group as the nucleophile to attack **2**. In this case, three dicarbolide groups per amine can be expected to add to the porphyrin. 5-(4-Aminophenyl)-5,10,15-triphenylporphyrin[20] (see Chapter 1) was refluxed with **2** in chloroform in the presence

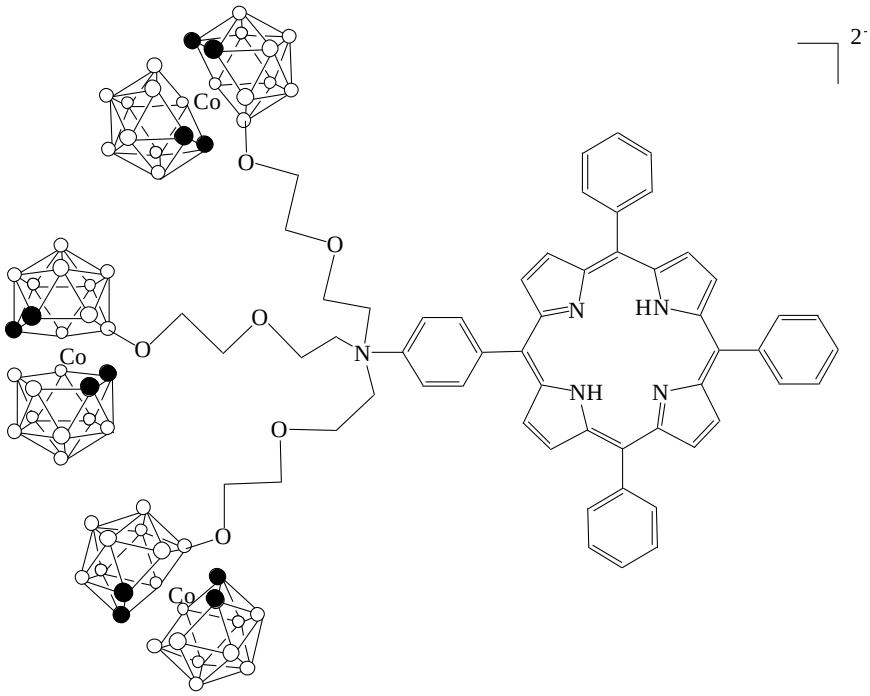
of inorganic base ($NaHCO_3$, as in *Scheme 2-4*). This reaction gave a complex mixture of products; besides recovering starting porphyrin and **2**, several green fractions and red-brown fractions were also obtained. MALDI-TOF MS indicated that the least polar green fraction had the same molecular weight as the more polar red-brown fraction. More interestingly, the most polar fraction from this reaction gave a very intense molecular weight peak at m/z 2364, which corresponds to four molecules of **2** added to one porphyrin. This indicates that the pyrrolenic nitrogen atom may also react with **2** under these conditions (see below).



Scheme 2-4: Syntheses **14** and **15**. Reaction Conditions: **2**, chloroform/acetonitrile = 1/2.

NMR spectroscopy showed the fraction to be a mixture of regioisomers (probably containing two cobaltacarboranes linked to the meso-aniline group and the others linked to the pyrrolenic nitrogens). Fortunately, the above reaction is solvent-dependent. When the reaction was done in

a mixture of chloroform and acetonitrile (v/v = 1:2), the *N*-substituted derivatives could not be detected.



16

As shown in *Scheme 2-4*, the reaction gave 46% of **14** and 26% of **15** as well as a small amount of starting 5-(4-aminophenyl)-5,10,15-triphenylporphyrin. It should be noted that the reaction proceeded very slowly in pure acetonitrile; it is believed that chloroform could accelerate the nucleophilic reaction. In order to obtain porphyrin **16**, excess amounts of **2**, different non-nucleophilic bases, and various solvents were tried, but failed to give **16**. The zinc(II) complex of 5-(4-aminophenyl)-5,10,15-triphenylporphyrin, which has lower reactivity compared to its metal-free porphyrin, also failed to give **16**. It seems that after adding two cobaltacarborane groups**,** the molecule is too sterically hindered to react with **2** to form **16**. However, a small amount of **16** was detected by MALDI-TOF MS when the reaction was done in pure $CHCl_3$. Tetrakis(4-aminophenyl)porphyrin was also allowed to react with excess **2**, but the reaction would not go to completion and gave a very complex mixture of product.

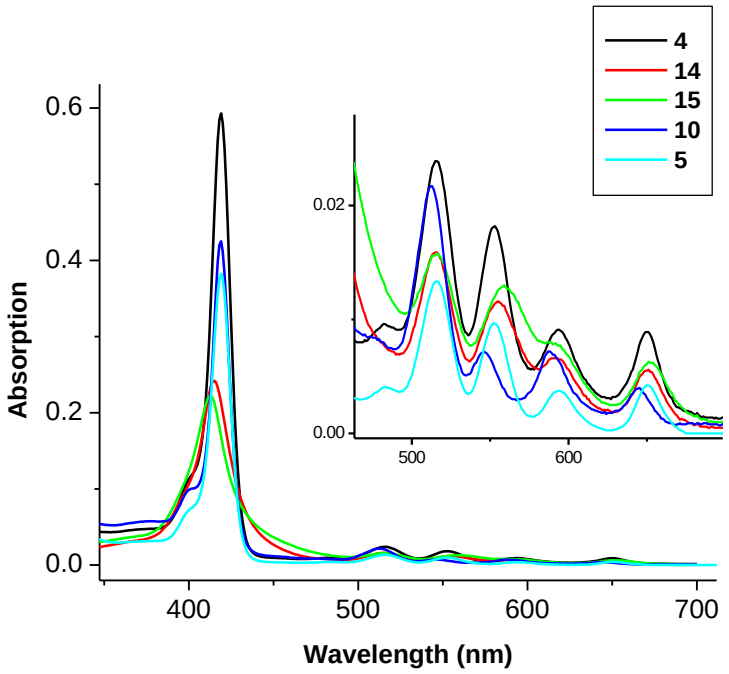


Figure 2-8: UV-vis spectra of porphyrins **14** and **15** with **4**, **5**, **10** in 1 μM acetone.

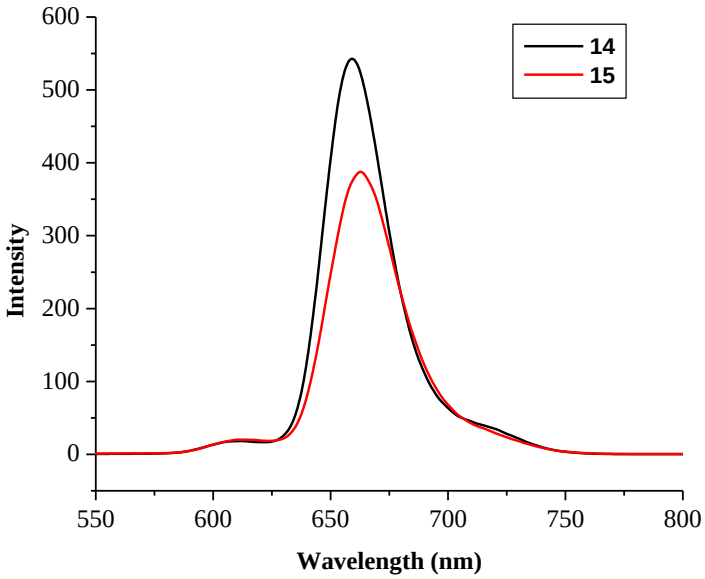
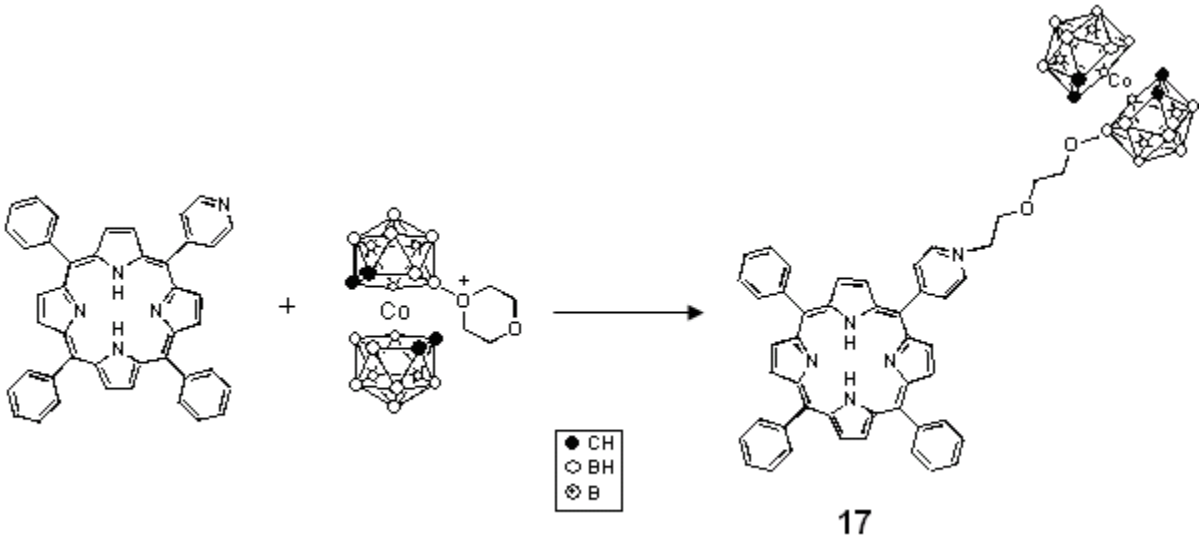


Figure 2-9: Fluorescence of porphyrins **14** and **15** in 1 μM acetone.

No further separation was done in this case. UV-vis spectra of **14** and **15** (*Figure 2-8*) show 4-5 nm blue shifts compared with the parent porphyrin. The low extinction coefficient as well as low intensity of fluorescence (*Figure 2-9*) may indicate some aggregation of these compounds in solution.

2.5 Porphyrin-Cobaltacarborane Conjugates from Pyridyl Containing Porphyrins

Several *N*-alkylated pyridylporphyrins, for example *meso*-tetrakis(*N*-methylpyridium-4-yl)porphyrin have been widely studied as model compounds for DNA binding[21]. These results showed that the binding mechanism could be modulated by the size and location of the peripheral groups, by the porphyrin charge, and by the nature of the metal ion in the porphyrin core. We are interested to know whether our zwitterionic porphyrin conjugates could demonstrate some structure/activity relationships as potential BNCT agents or even could present similar binding properties to DNA.



Scheme 2-5: Reaction conditions: $CHCl_3/CH_3CN$ (1:1), 60 ^oC, 12 h (98.4%).

By employing the ring-opening reactions described above, the porphyrin-cobaltacarborane conjugates **17-21** could be obtained in high yields by simply mixing the corresponding 4-

pyridyl/phenyl porphyrins with excess amounts of compound **2** in mixtures of chloroform and acetonitrile (*Scheme 2-5*).

Usually, the reaction is very clean and analytically pure target compounds could be obtained by washing the reaction residue with ethyl ether (to remove the excess compound **2)**. However, in some cases, especially when high temperature (70–80 ℃) or pure chloroform were used, small amount (sometimes, up to 10% by ^{1}H-NMR analysis) of some unidentified green compounds (maybe the *N*-substituted porphyrin derivatives) could be detected.

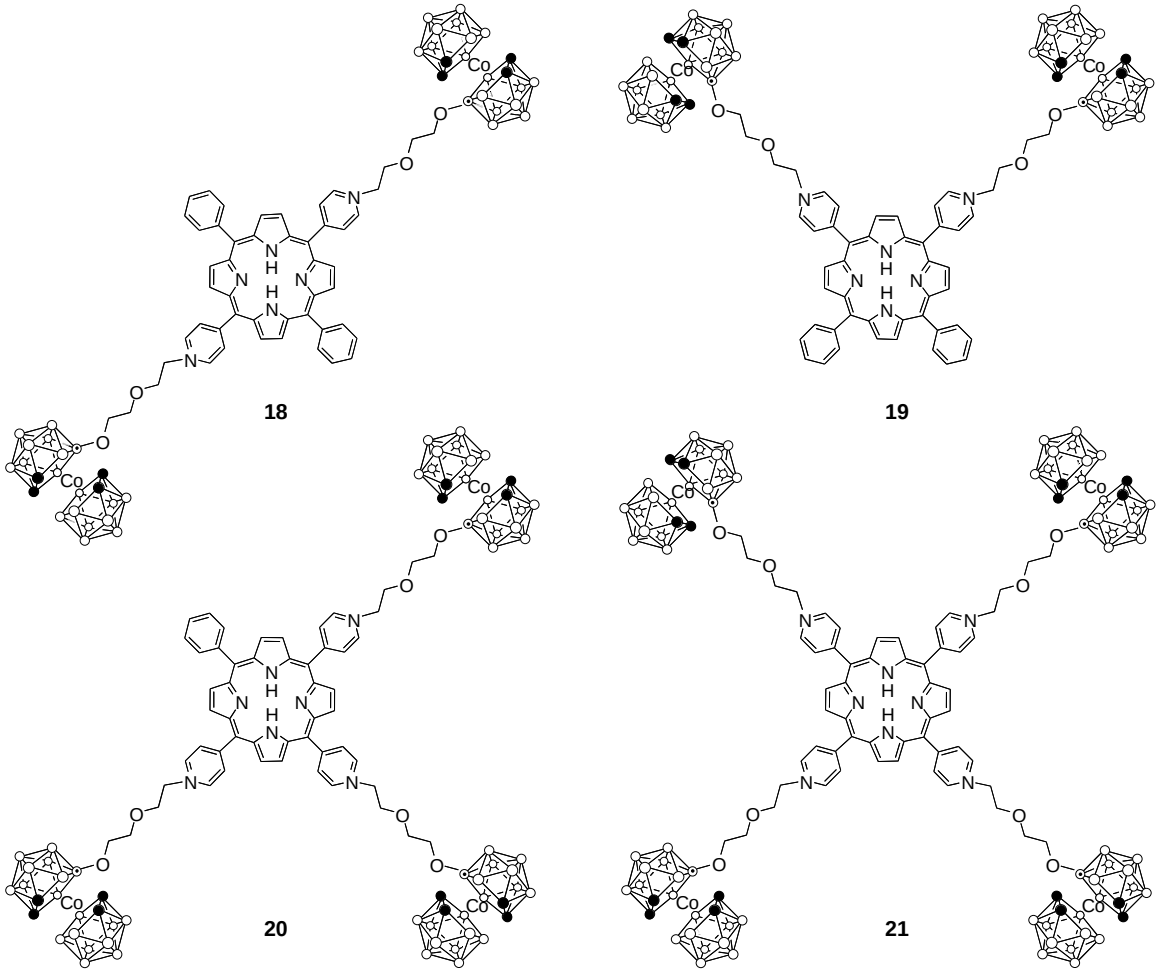


Figure 2-10: Structures of synthesized porphyrin-cobaltacarborane conjugates **18**-**21.**

Due to the solubility differences between the target conjugates and the byproducts produced in methanol, the target conjugates could be easily purified by washing with methanol to remove the byproducts. In this case, analytically pure conjugates could be obtained in high yields without chromatography. Through this efficient reaction, one can expect that it is easy to obtain large amounts of target conjugates. Also, this efficient method provides us with the possibility to easily obtain a series of conjugates for structure/activity relationship studies of porphyins carrying boron clusters for BNCT. The zwitterionic porphyrin conjugates **17-21** are very soluble in most polar organic solvents, such as DMSO, acetone, acetonitrile, ethyl acetate, THF, and DMF, but they have very limited solubility in either methanol or water because of the charge delocalization.

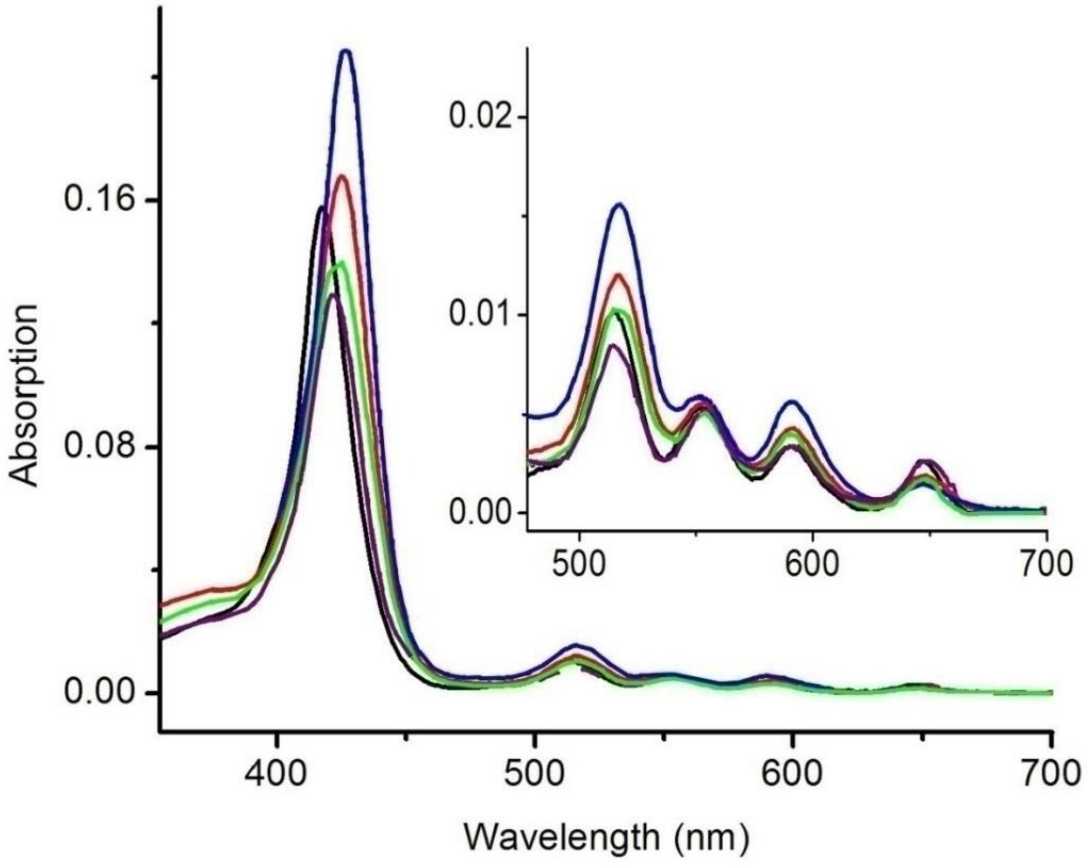


Figure 2-11: Optical spectra of conjugates **17-21** at 1 μM in acetone solution

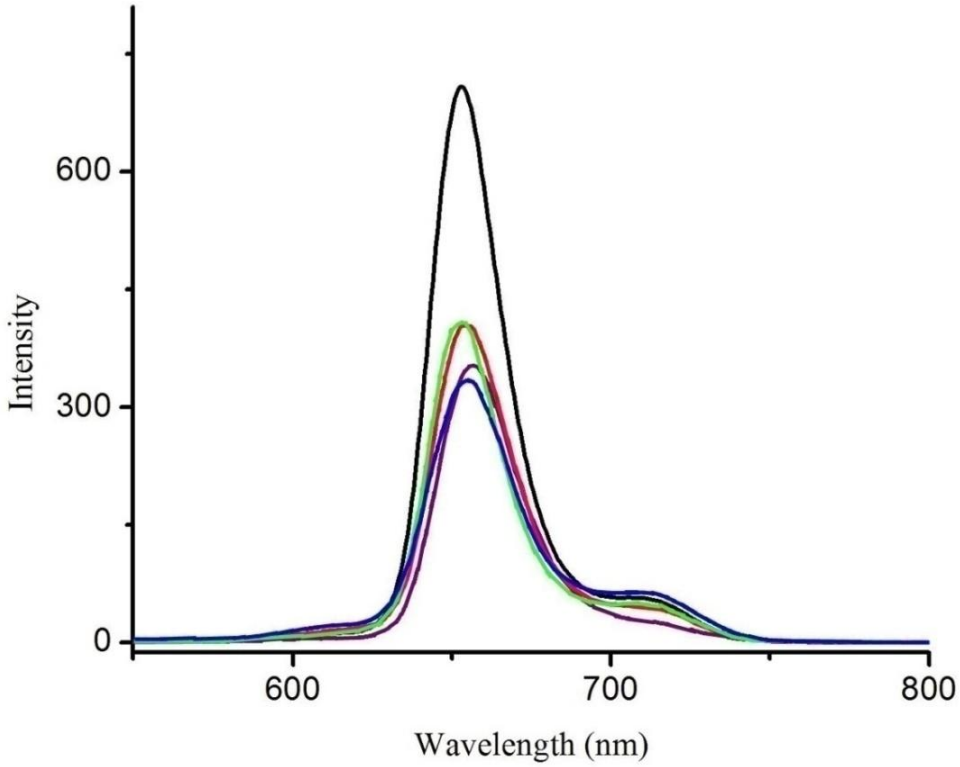


Figure 2-12: Fluorescence emission spectra of conjugates **17-21** at 1 μM in acetone solution upon excitation at 416 nm at room temperature.

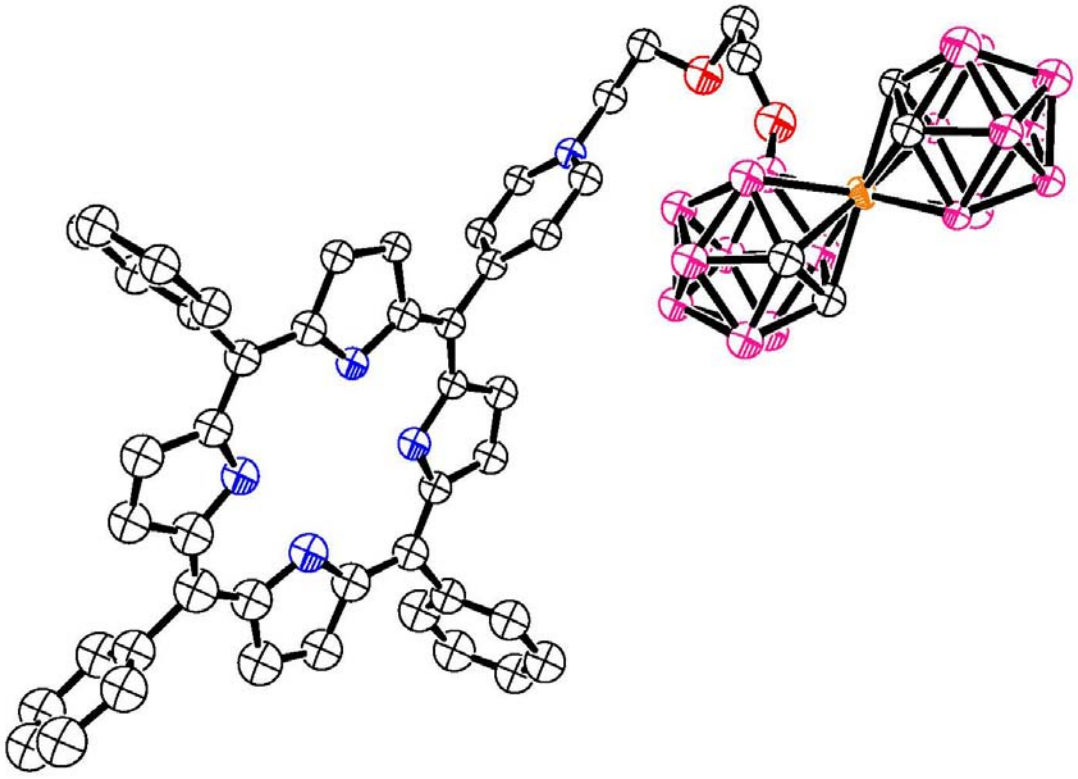


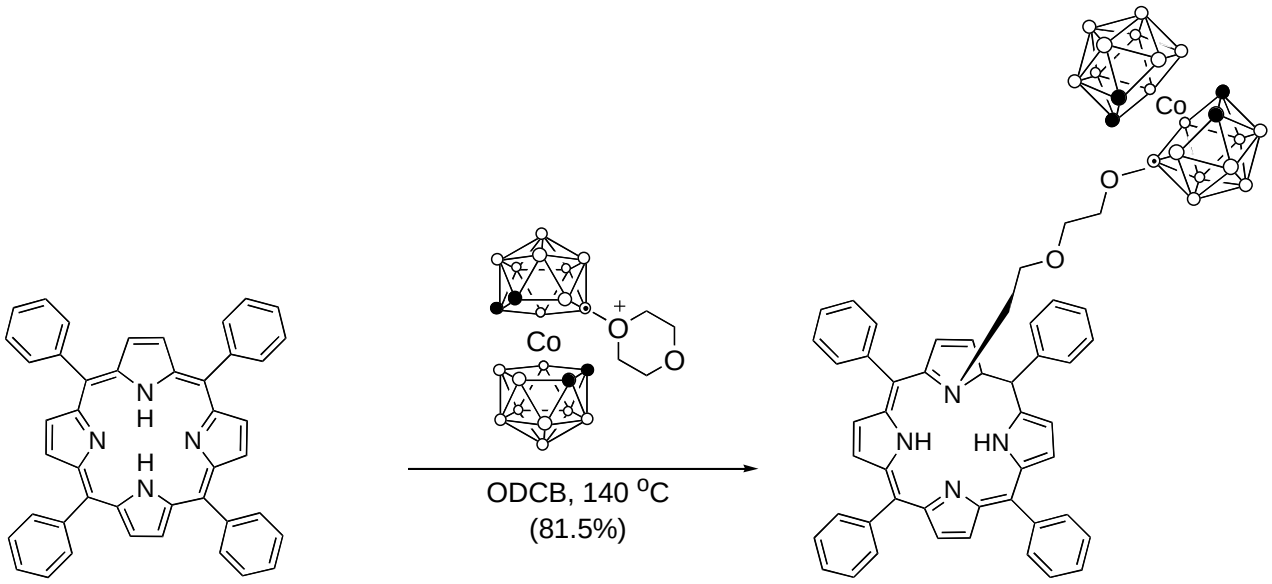
Figure 2-13: Molecular structure of porphyrin-cobaltacarborane **17**.

Their low extinction coefficients in acetone compared with the corresponding starting porphyrins may indicate the formation of small amount of aggregates even at the micromole concentration level, which may also be responsible for their poor solubility in methanol and water. The interesting aspect of the UV-vis spectra (*Figure 2-11*) of these conjugates is that there is a 2-3 nm red shift of the Soret band with increase in the number of the metallacarborane cages on the porphyrin macrocycles from 418 nm for conjugate **17** to 427 nm for compound **21**. The fluorescence spectra (*Figure 2-12*) of conjugates **17**-**21** display λ_{max} (emission) around 653 nm in acetone, which indicates the fluorescence properties in these conjugates and makes them easily detectable when applied for biological study. The molecular structure of conjugate **17** is shown in *Figure 2-13*. The porphyrin core is reasonably planar, having mean deviation of 24 atoms from the average plane of only 0.07Å and maximum deviation 0.18(2)Å. The two dicarbollide moieties coordinate to the Co atom with their five-member rings parallel. The Co atom is equidistant from the two five-member rings, having a perpendicular distance of 1.463(2) Å to the untethered dicarbollide and 1.464(2) Å to the tethered one. The centroid-Co-centroid angle is 178.3(1) °.

2.6 *N*-Substituted Porphyrin-Cobaltacarborane Conjugates

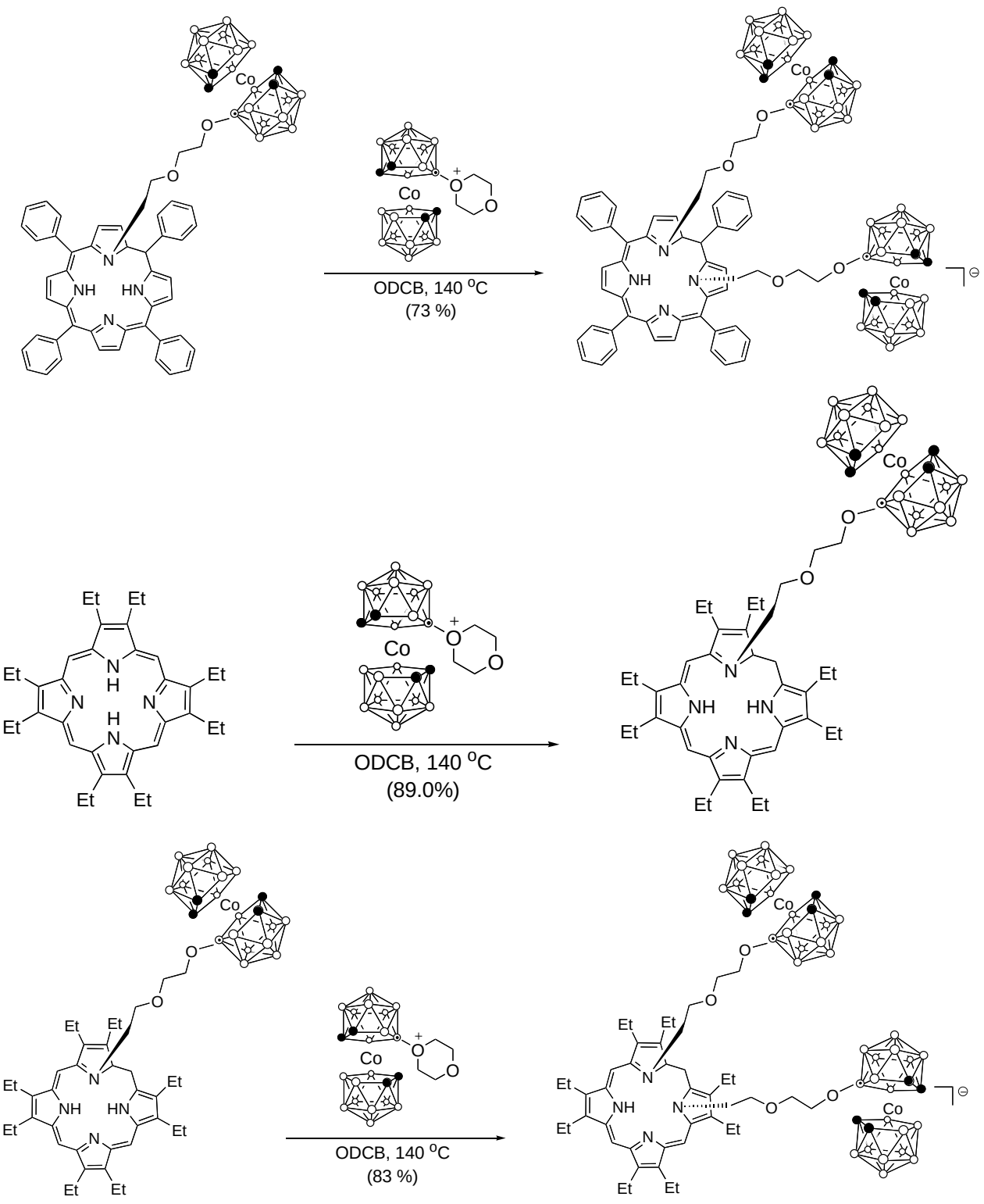
As mentioned above, **2** was found to react with the pyrrolenic nitrogen atoms of porphyrins to form *N*-substituted porphyrin derivatives. There remain limited methods to synthesize *N*-substituted porphyrins which could significantly lead to nonplanar conformations of porphyrin macrocycles. In order to simplify the reaction we selected *meso*-tetraphenylporphyrin (H_2TPP) to react with **2**, since *N*-methylated tetraphenylporphyrins have already been reported and are well-characterized[22]. To get the target *N*-substituted porphyrin-cobaltacarborane conjugates, H_2TPP was first refluxed with **2** in chloroform in the presence of $NaHCO_3$. The reaction occurred very

slowly and needed about 10 days to finish (according to the disappearance of H_2TPP from TLC monitoring). The reaction constantly gave 76~84% yields of **22** (*Scheme 2-6*).



Scheme 2-6: Synthesis of *N*-substituted porphyrin derivatives **22**.

When the reaction was done in ODCB at higher temperature (140 ℃), it was finished in two hours even without base and gave an 81% yield of **22**. Interestingly, under both reaction conditions, a small amount of di-substituted derivative was isolated and the structure is proposed to be **23,** by comparing its NMR, MS and UV-vis spectra with similar ones in the literature[22, 24]. HRMS-MALDI-TOF MS gave an exact mass for compound **22** as 1025.5717 and for **23** as 1458.8850. H^1-NMR spectra of **22** are similar to the monocation of *N*-substituted H_2TPP derivatives, giving a NCH_2 peak at –4.83 ppm. Unlike common *N*-alkylporphyrins, **22** and **23** are both extremely basic and could only be isolated as their green mono-cation forms. Attempts to deprotonate them by using pyridine or even sodium hydroxide failed. Similar reactions was also succeed with octaethylporphyrin (*Scheme 2-7*), giving porphyrin **24** in 89% yield. Further reaction starting from **22** or **24** gave di-substituted porphyrins **23** and **25** in 73% and 83% yields, respectively.



Scheme 2-7: Synthesis of *N*-substituted porphyrin derivatives **23** (top)**, 24** (middle) and **25** (bottom).

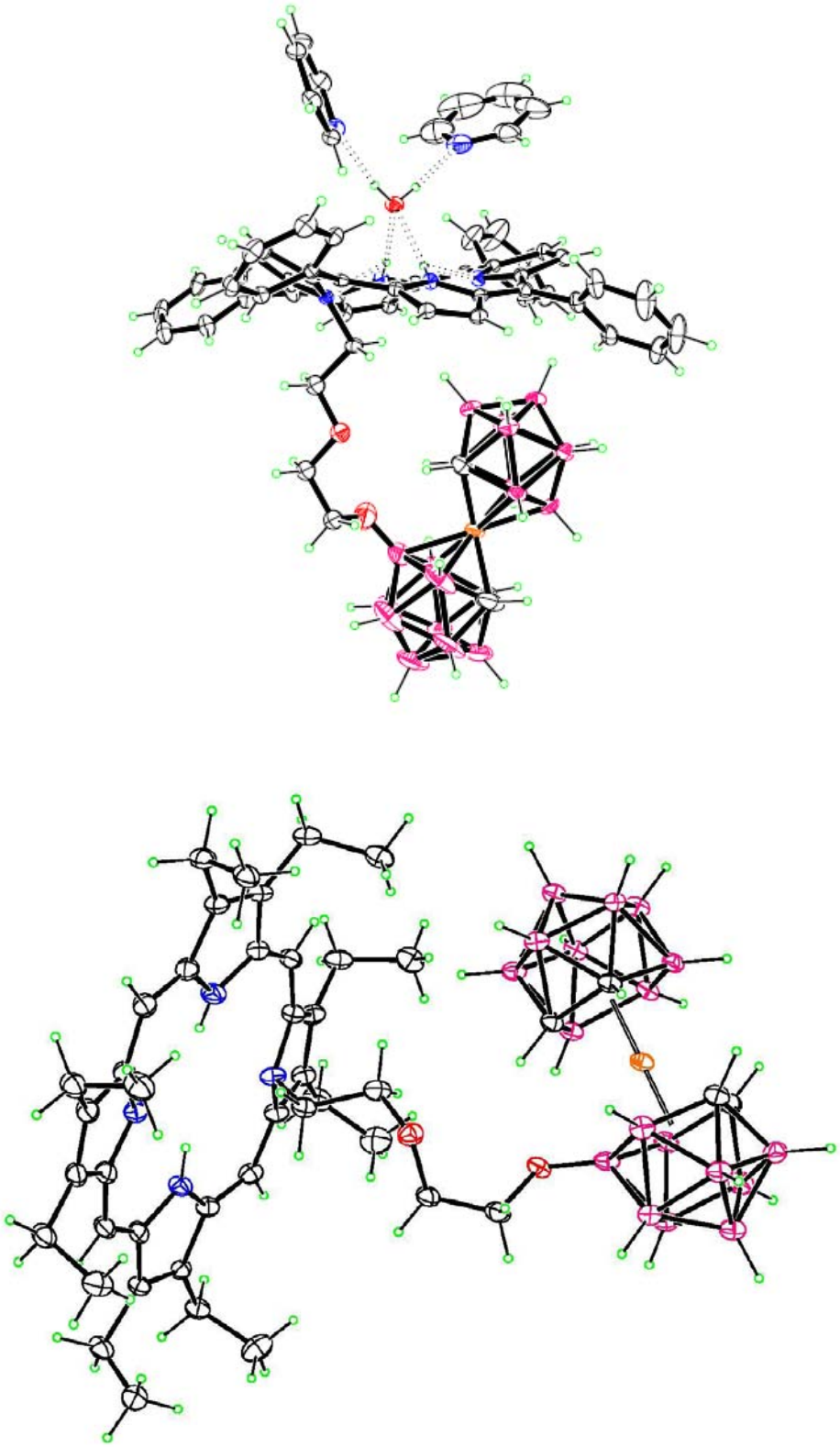


Figure 2-14: X-Ray structures of porphyrins **22** (top) and **24** (bottom).

The crystal structure of **22** (*Figure 2-14*) further confirmed the structure of the *N*-substituted porphyrin **22**, a rare example of a free-base mono-cation *N*-substituted porphyrin[13]. The crystal was grown in pyridine layered by cyclohexane. Due to the negative charge of cobaltacarborane, **22** is actually a neutral compound as an intramolecular ammonium salt. The two protonated pyrrolenic rings are located adjacent to the alkylated ring and are rotated in the opposite sense. Interestingly, the two hydrogen atoms of the two protonated pyrrolenic rings form hydrogen bonds with one water molecule, while at the same time; the water molecule forms another two hydrogen bonds with another two pyridine molecules. In contrast, the crystal structure of **25** shows much less distortion of the porphyrin core plane as shown in *Figure 2-14*.

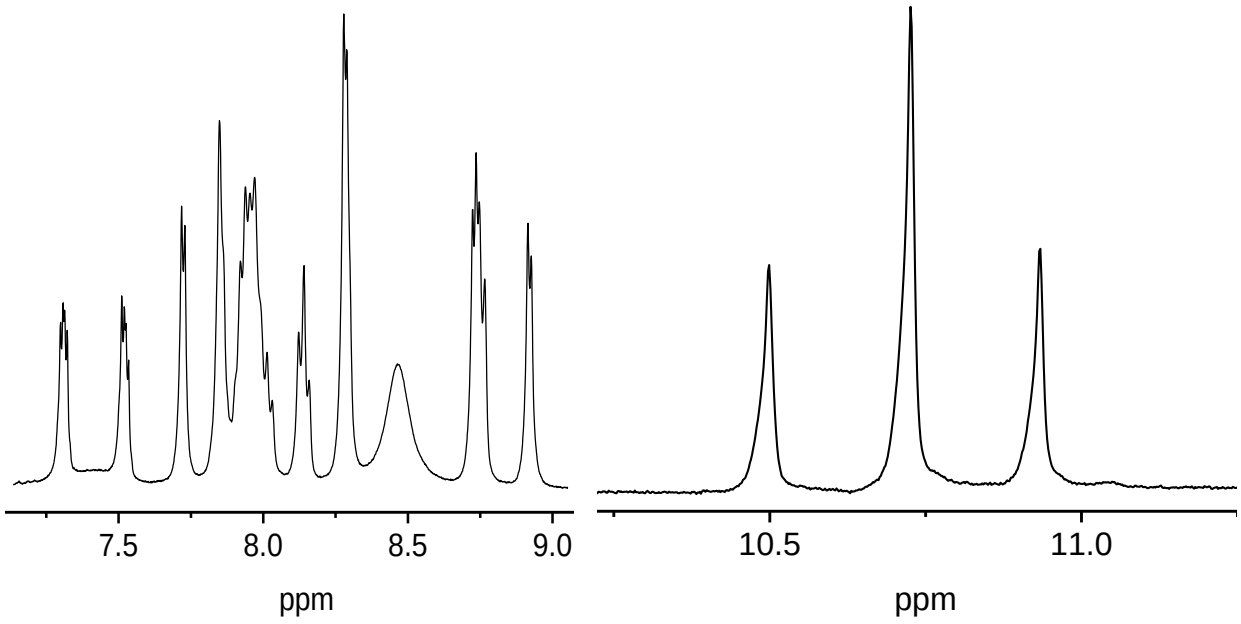


Figure 2-15: ^{1}H-NMR spectra (aromatic region only) of porphyrin **23** in acetone-d_6 at 400 MHz. ^{1}H-NMR (left), of porphyrin **25** in acetone-d_6 at 250 MHz (right).

The H^{1}-NMR spectrum of porphyrin **24** shows two singlet resonances for the four *meso*-protons, split into 1:1 and giving peaks at 10.67 and 10.61 ppm, respectively. The NCH_2 signals

of porphyrin **4** appear at –5.57 ppm. In contrast, compound **23** gave two different N-CH_2 peaks at –5.80 and –4.25 ppm, respectively, and one NH peak at –2.64 ppm. The ^{1}H-^{1}H COSY NMR spectrum for porphyrin **23** shows that the two hydrogen atoms of the NCH_2 are in different environments and are split into two peaks at –5.80 and –4.25 ppm. The symmetry observed in the ^{1}H-NMR spectra of porphyrin **23** indicates that the two alkylated nitrogen atoms are adjacent to each other. The aromatic region of the H^1-NMR of porphyrin **23** is shown in *Figure 2-15*. The eight protons in the porphyrin *beta* positions spit into a 2:4:2 multiplet. Similarly, the H^1-NMR spectrum of porphyrin **25** shows three resonances for the *meso*-protons, split into a 1:2:1 pattern (*Figure 2-1*5), which further indicates that the two substituents are on adjacent nitrogen atoms. The regioselective formation of porphyrins **23** and **25** is remarkable, but is nonetheless precedenedt[22-24]. *N*-Substituted derivatives of tetraphenylporphyrin and octaethylporphyrin with different methylation reagents have, for a long time, been studied and are all in agreement with this regioselectivity because the dialkylation was believed to take place from the less sterically hindered side. The geometry was confirmed by X-ray structure in two cases[24].

It has long been known that the bathochromic shift of the absorption of porphyrins correlates with the degree of conformational distortion. *N*-Substitution is known to increase the degree of nanplanarity of porphyrins. This is evident in the absorption spectra of porphyrins **22- 25** shown in *Figure 2-16*. There are significant (15-32 nm) red-shifts of the Soret bands for the *N*-substituted H_2TPP derivatives **22** and **23** compared with the H_2TPP**,** which is believed to be the distortion effect from *N*-substitution of the porphyrin macrocycle.

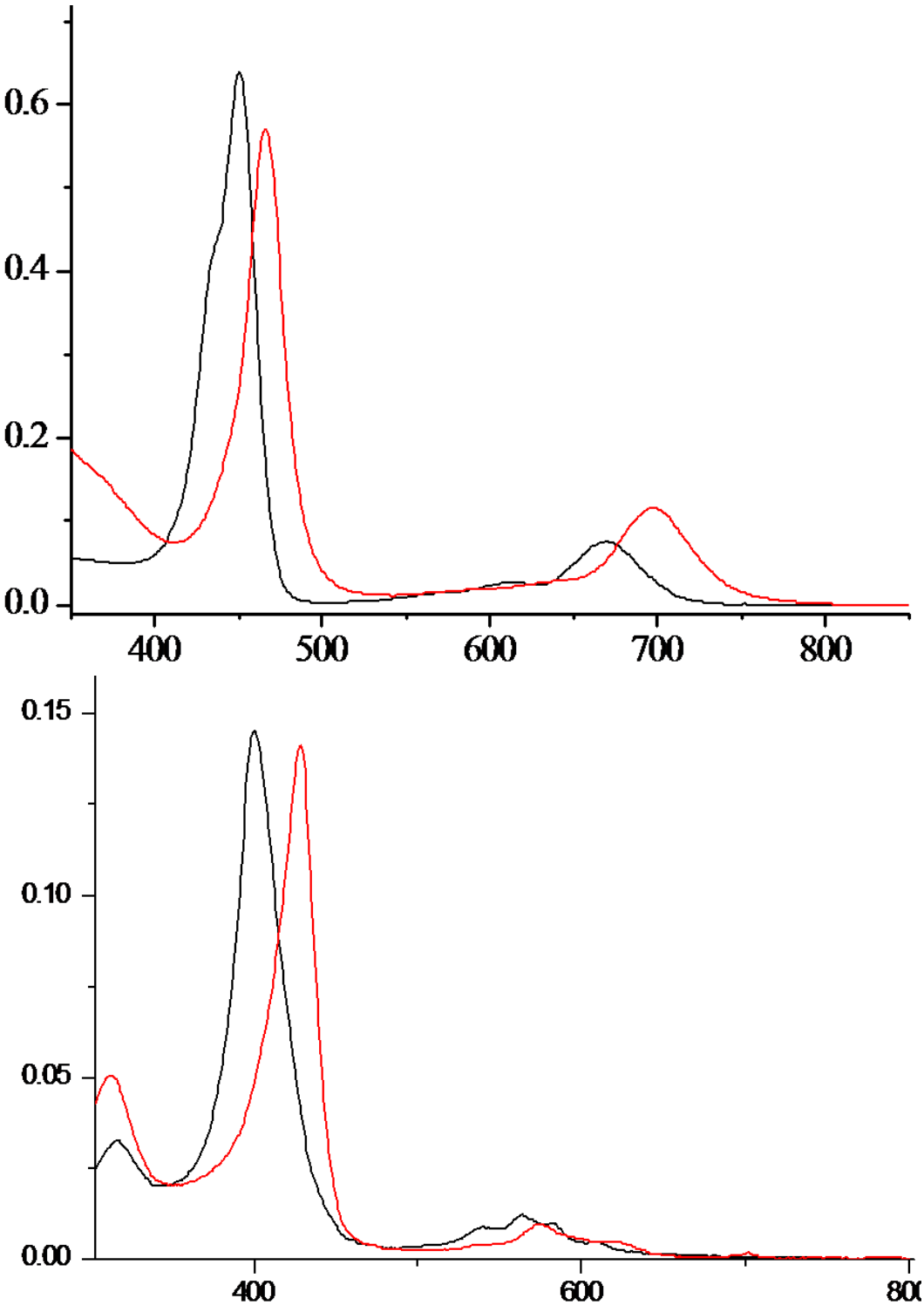


Figure 2-16: UV-vis spectra of **22** (black) and **23** (red) in acetone at 2×10^{-6} M (left); UV-vis spectra of **24** (black) and **25** (red) in acetone at 1×10^{-6} M (right).

The same trend was found in porphyrins **24** and **25**, when compared with H_2OEP. The fluorescence emission spectra (*Figure 2-17*) of porphyrins **22-25** are nearly completely quenched (more than 90% compared with porphyrins **1** and **2**) due to the strong distortions of the porphyrin conformation by the cobaltocarboranes attached to the central nitrogen atom.

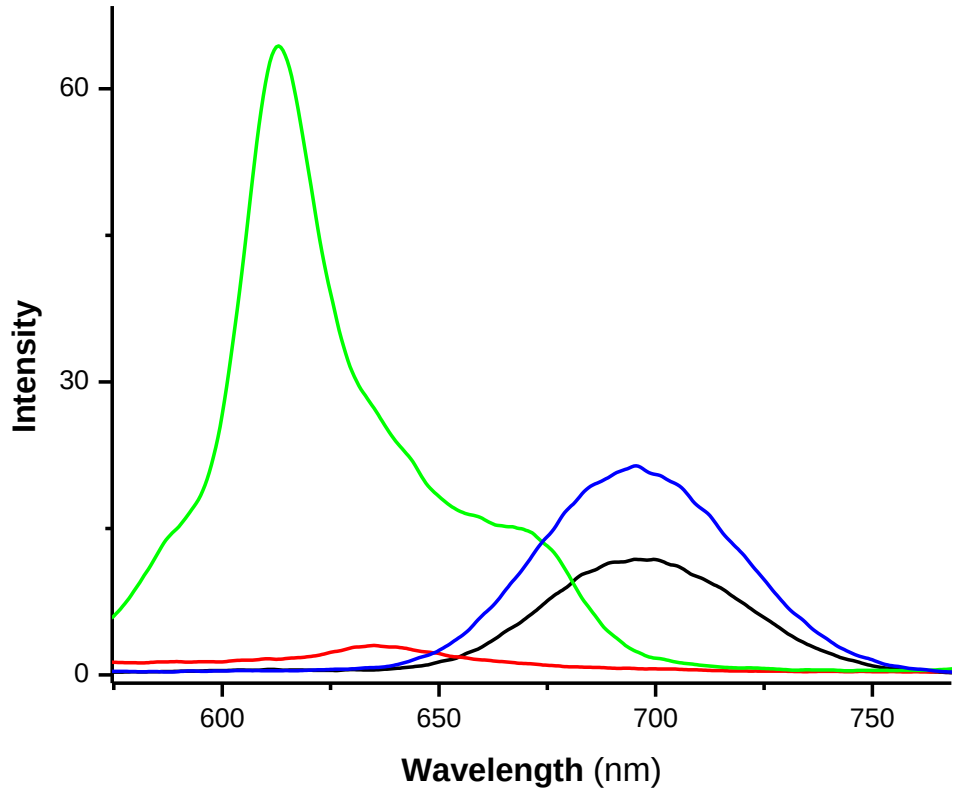


Figure 2-17: Fluorescence spectra of **22** (blue), **23** (black), **24** (green) and **25** (red) in acetone at 1×10^{-6} M.

2.7: Biological Evaluations of Conjugates

Biological evaluations of these series of compounds were conducted in our laboratory in collaboration with Dr. Sibrian-Vazquez and Tim Jensen; there were also collaborations with other laboratories. Details of these results can be found in the publications[7,25]. Here, only a brief summary is presented. In our laboratory, cellular studies were performed, including cellular

uptake, cytotoxicity (dark and photo-), and preferential sites of subcellular localization of the conjugates; these were evaluated in human carcinoma HEp2 cells and in other cells. All the compounds localize preferentially within the cell lysosomes. The extent of conjugate uptake depends on the number of carborane clusters at the porphyrin periphery, the geometry of the molecule, and the nature of aggregates formed. All conjugates showed no dark toxicity and very low phototoxicity, probably due to aggregation and subsequent quenching of singlet oxygen generation. Some conjugates (such as **17**-**21**) needed a delivery vehicle, such as Chromospheres, because of their low solubility in water. Animal studies of compound **10** were performed within or collaborative research group and showed that it has no dark toxic effect for mice up to 160 mg/kg (compound dose/mouse weight), which is the highest dose we tested in our experiments. Uptake data of compound **7** from our collaborative research group in Japan using different cell lines (C6: rat glioma; U87delta: human glioma; f5 and IOMM-Lee: human meningioma) gave very encouraging results: compound **7** shows 50-100 times more uptake, compared to the clinical trial compound BPA, when exposed to 20 ppm boron containing medium for 24 hours.

In conclusion, the efficient syntheses and characterizations of series of porphyrin-cobatacarborane conjugates containing 1 to 8 cobaltacarborane clusters per porphyrin from readily available porphyrins are described. Both meso-substituted and N-substituted conjugates were synthesized. Most of these dendrimer-like compounds contain high percentages of boron, are fluorescent and are water-soluble. Prelimary *in-vitro* and *in-vivo* studies showed that they are highly promising candidates for BNCT. The synthetic method described here has opened an efficient way to prepare high percentage boron-containing porphyrins and their analogs. In some cases, chromatography was not needed. The cobalt ion in the sandwich can potentially be radio

labeled and used as novel MRI reagents. Electrochemical studies of this series of compounds were evaluated in Dr. Kadish's laboratory in the University of Houston.

2.8. Experimental

Syntheses. All reactions were monitored by TLC using 0.25 mm silica gel plates with or without UV indicator (60F-254). Silica gel (Sorbent Technologies 32-63 μm) was used for flash column chromatography. HPLC analyses were carried out on a Dionex system including a P680 pump and a UVD340U detector, using a Delta Park C_{18} 300 Å, 5 um, 3.9 × 150 mm (Waters) column and stepwise gradient conditions. Two solvent systems were used: (a) buffer A (5% acetonitrile, 0.1% TFA, H_2O) and buffer B (5% H_2O, 0.1 % TFA, acetonitrile), for compounds **4**-**10**; (b) acetonitrile and methanol. ^{1}H- and ^{13}C-NMR spectra were obtained on either a DPX-250 or an ARX-300 Bruker spectrometer. Chemical shifts (δ) are given in ppm relative to residual protons in actone-d_6 (2.05 ppm, ^{1}H; 206.0 ppm, ^{13}C) unless otherwise indicated. Electronic absorption spectra were measured on a Perkin Elmer Lambda 35 UV-Vis spectrophotometer and fluorescence spectra were measured on a Perkin Elmer LS55 spectrometer. Mass spectra were obtained on an Applied Biosystems QSTAR XL. All solvents were obtained from Fisher Scientific (HPLC grade, Houston, TX) without further purification. $Cs[Co(C_2B_9H_{11})_2]$ was obtained from commercial sources.

Synthesis of 2: To 0.90 g (2.0 mmol) of Cs[3,3'-Co(1,2-$C_2B_9H_{11})_2$], **1**, in 100 mL of 1,4-dioxane was added 2.0 mL (16.0 mmol) of Et_2O BF_3 and the reaction mixture was heated at reflux under an N_2 atmosphere for 5 h. The solution was cooled to room temperature, filtered, and evaporated to dryness. The residue was taken up in DCM and passed through silica column using 30% DCM in hexane as the eluting solvent. The first fraction (small amount) was collected and identified as compound **3**. Then solvent was changed to DCM to elute the major fraction, identified as

compound **2**. The solutions were evaporated under vacuum, giving 81% yield for compound **2** as an orange solid, for which the ^{1}H NMR spectra were identical with those of an authentic sample prepared according to the literature[6a]. Compound **3** was isolated in 4% yield, its structure was confirmed by X-ray crystallography (grown by slow evaporation from DCM solution) and the ^{1}H NMR spectra were identical with those available in the literature[6c].

Synthesis of 4: Tetra(4-hydroxyphenyl)porphyrin (34.0 mg, 0.05 mmol) and K_2CO_3 (56.0 mg, 0.4 mmol) were refluxed (60 ℃ oil bath) in 10 mL acetone in a 50 mL round bottom flask under argon for 15 min. The reaction mixture was cooled to room temperature and compound **2** (103.1 mg, 0.25 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2 h and then refluxed overnight. Then another portion of K_2CO_3 (28 mg, 0.2 mmol) and **2** (63 mg, 0.15 mmol) were added to the mixture. The reaction mixture was refluxed overnight and the reaction was stopped (TLC or HPLC indicated only one porphyrin existed in the reaction mixture). The solvents were evaporated and the residue was dissolved in ethyl acetate. The solution was washed with water and the organic layer was evaporated to dryness. The residue was then washed with ether (5 × 5 mL) to remove excess **2** and byproducts (from the reaction of **2** and K_2CO_3). The brown solid was dried under vacuum at 50 ℃ for 2 d to give the target compound 106.1 mg (0.043 mmol) in 85.4% yield. HRMALDI-TOF-MS for $C_{76}H_{142}B_{72}Co_4K_4N_4O_{12}$: Calcd. 2411.4855 $[M-4K+4Na+H]^+$, found 2411.4881. ^{1}H-NMR (acetone-d_6, 300 MHz) □ 8.94 (s, 8H), 8.17 (d, 8H, J = 8.5 Hz), 7.43 (d, 8H, J = 85 Hz), 4.48 (s, 8H), 4.37 (s, 8H), 4.30 (s, 8H), 4.05 (s, 8H), 3.76 (d, 16H), 1.6-3.0 (br, 68H, BH), -2.70 (s, 2H, NH). ^{13}C-NMR (acetone-d_6, 75 MHz) d 160.5, 136.8, 135.7, 121.3, 114.4, 73.6, 71.0, 69.9, 69.3, 55.9, 47.9. UV-Vis (acetone) λmax (nm) 419 (□ 383 000), 516 (13 700), 552 (9900), 595 (3900), 651 (4600). HPLC t_R = 13.93.

Synthesis of 5: The method used is similar to that for compound **4**. 4-Hydroxybenzaldehyde (1 mmol, 122 mg), K_2CO_3 (1.1 mmol, 150 mg) and compound **2** (1 mmol, 411 mg) were mixed in 20 mL acetone at room temperature overnight. TLC indicated no starting material left. The mixture was dried under vacuum and passed through a silica gel plug eluting with EtOAc/acetone (1: 1) to give the target compound in 90% yield. MALDI-TOF m/z 532.9 $(M-K)^+$. ^{1}H-NMR (acetone-d_6, 300 MHz), 9.91 (s, 1H), 7.88 (d, 2H, J = 8.7 Hz), 7.15 (d, 2H, J = 8.7 Hz), 4.27 (t, 6H), 3.86 (t, 2H), 3.60 (s, 4H), 1.6-3.0 (br, 18H, BH). ^{13}C-NMR (acetone-d_6, 75 MHz) 191.3, 163.6, 132.8, 129.6, 114.9, 71.4, 68.8, 68.3, 67.9, 51.9, 46.1.

Synthesis of 6: 5-(3,5-Dihydroxyphenyl)-10,15,20-triphenylporphyrin (32.3 mg, 0.05 mmol) and K_2CO_3 (28.5 mg, 0.21 mmol) were refluxed (60 ℃ oil bath) in 10 mL acetone in a 50 mL round bottom flask under argon for 15 min. The reaction mixture was cooled to room temperature and compound **2** (41.2 mg, 0.1 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2 h and then refluxed overnight. The reaction mixture was then treated similarly to that described above for **4** (added another portion of 11.5 mg of **2** to drive the reaction to completion). After washing with ether and drying under vacuum at 50 ℃ for 2 d the target compound 54.1 mg (0.035 mmol) was obtained in 70.1 % yield. The low yield is due to the slight solubility of the target compound in ether). Column chromatography on silica gel using a mixture of ethyl acetate and acetone for elution gave a high yield of the target compound (75.1 mg, 97.2 % yield). MALDI-TOF-MS for $C_{60}H_{86}B_{36}Co_2K_2N_4O_6$: m/z Calcd. 1545.556 $[M+H]^+$, found 1545.405; 1583.648 $[M+K]^+$, found 1583.533. HR-ESI-MS for $C_{60}H_{85}B_{36}Co_2N_4O_6$: Calcd. 732.9379, found, 732.9421(two charges). ^{1}H-NMR (acetone-d_6, 250 MHz): 9.06 (d, 2H, β-H), 8.87 (m, 6H, β-H), 8.26 (m, 6H, o-phenyl-H), 7.84 (m, 9H, m, p-phenyl-H), 7.49 (d, 2H, o-Ar-H), 7.08(d, 2H, p-Ar-H), 4.40 (t, 4H, OCH_2), 4.23 (t, 8H, OCH_2), 3.92 (t, 4H, OCH_2), 3.66 (s, 8H,

car-H), 1.6-3.0 (br, 34H, BH), -2.76 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 63 MHz) 159.1, 144.4, 142.8, 135.1, 128.6, 127.6, 120.8, 120.7, 115.3, 101.8, 72.8, 70.1, 69.1, 68.7, 54.7, 47.1. UV-vis (acetone) λmax (nm) 415 (ε 318 600), 511 (14 000), 544 (5400), 589 (3800), 646 (3200). HPLC t_R = 5.97.

Synthesis of 7: 5,15-Di(3,5-dihydroxyphenyl)-10,20-diphenylporphyrin (34.2 mg, 0.05 mmol) and K_2CO_3 (54.9 mg, 0.40 mmol) were refluxed (60 ℃ oil bath) in 20 mL acetone in a 50 mL round bottom flask under argon for 15 min. The mixture was cooled to room temperature and compound **2** 82.2 mg (0.20 mmol) was added. The reaction was then treated as above (another 2 portions 20.0 mg and 20.1 mg of **2**, respectively, were added to drive the reaction to completion). After washing with ether and drying under vacuum, the target porphyrin 111.4 mg (0.045 mmol) was obtained in 89.8% yield. MALDI-TOF-MS for $C_{76}H_{142}B_{72}Co_4K_4N_4O_{12}$: Calcd. 2410.944 $[M-4K+4Na+H]^+$, found 2410.985. HR-ESI-MS for $C_{76}H_{141}B_{72}Co_4N_4O_{12}$: Calcd. 579.3782, found, 579.3815 (four charges). ^{1}H-NMR (acetone-d_6, 250 MHz): 9.02 (d, 4H, β-H), 8.86 (d, 4H, β-H), 8.27 (m, 4H, o-phenyl-H), 7.84 (m, 6H, m, p-phenyl-H), 7.50 (s, 4H, o-Ar-H), 7.08(s, 2H, p-Ar-H), 4.41 (t, 8H, OCH_2), 4.19 (s, 16H, OCH_2), 3.94 (t, 8H, OCH_2), 3.68 (s, 16H, car-H), 1.6-3.0 (br, 68H, BH), -2.77 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 63 MHz) 159.1, 144.5, 142.7, 135.1, 128.6, 127.6, 120.8, 120.7, 115.2, 101.7, 72.8, 70.1, 69.1, 68.6, 54.4, 47.2. UV-vis (acetone) λmax (nm) 417 (ε 495 700), 512 (23 000), 546 (9100), 588 (4300), 645 (600). HPLC t_R = 15.16.

Synthesis of 8: 5,10-Di(3, 5-dihydroxyphenyl)-15,20-diphenylporphyrin (17.2 mg, 0.025 mmol) and K_2CO_3 (28.1 mg, 0.20 mmol) were refluxed (60 ℃ oil bath) in 10 mL acetone in a 50 mL round bottom flask under argon for 15 minutes. The reaction mixture was cooled to room temperature and compound **2** (60.3 mg, 0.15 mmol) was added. The reaction was then treated as described above (another two portions 11.0 mg and 10.3 mg of **2**, respectively, were added to

drive the reaction to completion). After washing with ether and drying under vacuum, the target porphyrin 57.1 mg (0.023 mmol) was obtained in 91.3% yield. MALDI-TOF-MS for $C_{76}H_{142}B_{72}Co_4K_4N_4O_{12}$: Calcd. 2410.944 $[M-4K+4Na+H]^+$, found 2410.553; Calcd. 2432.926 $[M-4K+5Na]^+$, found 2433.100. HR-ESI-MS for $C_{76}H_{141}B_{72}Co_4N_4O_{12}$: Calcd. 579.3782, found, 579.3838 (four charges). ^{1}H-NMR (acetone-d_6, 250 MHz): 8.99 (s, 4H, β-H), 8.81 (d, 4H, β-H), 8.22 (m, 4H, o-phenyl-H), 7.80 (m, 6H, m, p-phenyl-H), 7.45 (d, 4H, o-Ar-H), 7.05(s, 2H, p-Ar-H), 4.37 (t, 8H, OCH_2), 4.15 (s, 16H, OCH_2), 3.91 (t, 8H, OCH_2), 3.64 (s, 16H, car-H), 1.6-3.0 (br, 68H, BH), -2.81 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 63 MHz) 159.1, 144.5, 142.7, 135.1, 128.6, 127.5, 120.9, 120.6, 115.2, 101.8, 72.9, 70.1, 69.1, 68.7, 54.4, 47.2. . UV-vis (acetone) λmax (nm) 417 (ε 421 500), 512 (19 500), 546 (5500), 588 (4300), 645 (2900). HPLC t_R = 12.22.

Synthesis of 9: 5,10,15-Tris(3, 5-dihydroxyphenyl)-20-phenylporphyrin (11.8 mg, 0.017 mmol) and K_2CO_3 (28.0 mg, 0.20 mmol) were refluxed (60 ℃ oil bath) in 10 mL acetone in a 50 mL round bottom flask under argon for 15 minutes. The reaction mixture was cooled to room temperature and compound **2** (42.0 mg, 0.10 mmol) was added. The reaction was then treated as above (another two portions of 21.0 mg of **2** were added to drive the reaction to completion). After washing with ether and drying under vacuum, the target porphyrin 52.8 mg (0.016 mmol) was obtained in 93.4% yield. MALDI-TOF-MS for $C_{92}H_{198}B_{108}Co_6K_6N_4O_{18}$: Calcd. 3405.212 $[M+H]^+$, found 3405.342; Calcd. 3428.202 $[M+Na+H]^+$, found 3428.271; Calcd. 3444.312 $[M+K+H]^+$, found 3445.391. HR-ESI-MS for $C_{92}H_{199}B_{708}Co_6N_4O_{18}$: Calcd. 5283596, found, 528.3658 (six charges). ^{1}H-NMR (acetone-d_6, 250 MHz): 9.00 (s, 6H, β-H), 8.85 (d, 2H, β-H), 8.26 (m, 2H, o-phenyl-H), 7.84 (m, 3H, m, p-phenyl-H), 7.48 (s, 6H, o-Ar-H), 7.08(s, 3H, p-Ar-H), 4.40 (t, 12H, OCH_2), 4.18 (s, 24H, OCH_2), 3.94 (t, 12H, OCH_2), 3.68 (s, 24H, car-H), 1.6-3.0 (br, 102H, BH), -2.81 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 63 MHz) 159.1, 144.5, 142.7, 135.1,

128.6, 127.5, 120.9, 120.6, 115.2, 101.8, 72.9, 70.1, 69.1, 68.7, 54.4, 47.2. UV-vis (acetone) λmax (nm) 418 (ε 396 100), 512 (19 500), 546 (7400), 588 (7200), 644 (4700). HPLC t_R = 11.61.

Synthesis of 10: 5,10,15,20-Tetra(3,5-dihydroxyphenyl)porphyrin (18.9 mg, 0.025 mmol) and K_2CO_3 (500.0 mg, 3.62 mmol) were refluxed (60 ℃ oil bath) in 20 mL acetone in a 50 mL round bottom flask under argon for 15 minutes. The reaction mixture was cooled to room temperature and compound **2** (100.0 mg, 0.25 mmol) was added. The reaction was then treated as above (added another two portions 40 mg and 21 mg of **2**, respectively, were added to drive the reaction to completion). After washing with ether and drying under vacuum, gave the target porphyrin 104.2 mg (0.024 mmol) in 94.5% yield. MALDI-TOF-MS for $C_{108}H_{254}B_{144}Co_8K_8N_4O_{24}$: m/z Calcd. 4335.040 $[M+H]^+$, found 4335.507; 4374.140 $[M+H+K]^+$, found 4374.678. HR-ESI-MS for $C_{108}H_{255}B_{144}Co_8N_4O_{24}$: Calcd. 502.8503, found, 502.8544 (eight charges). ^{1}H-NMR (acetone-d_6, 250 MHz): 8.99 (s, 8H, β-H), 7.45 (s, 8H, o-Ar-H), 7.08 (s, 4H, p-phenyl-H), 4.39 (t, 16H, OCH_2), 4.21 (br, 32H, OCH_2), 3.93 (t, 16H, OCH_2), 3.68 (s, 32H, car-H), 1.6-3.0 (br, 136H, BH), -2.82 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 63 MHz) 159.5, 144.9, 121.0, 115.6, 102.3, 73.2, 70.6, 70.2, 69.6, 55.0, 47.6. UV-vis (acetone) λmax (nm) 419 (ε 425 200), 512 (21 700), 546 (7200), 587 (7200), 645 (4,000). HPLC t_R = 5.66.

Synthesis of 11: This conjugate was prepared from 5,10,15-Tris(4-hydroxyphenyl)-20-(4-methoxyphenyl)porphyrin (Chapter 1) and [3,3'-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$(1',2'-$C_2B_9H_{10}$)] **2**, as described above and the product was obtained in 93% (64.2 mg) yield, mp = 230 ^{o}C (dec). HPLC t_R = 11.04 min. UV-vis (acetone) λ_{max} (ε/(M^{-1} cm^{-1})) 419 (593000), 516 (23900), 553 (18000), 593 (9000), 651 (8900). ^{1}H NMR (acetone-d_6, 250 MHz): δ 8.91-8.94 (m, 8H, β-H), 8.14 (d, 8H, *J* = 7.9 Hz, *o*-PhH), 7.34-7.37 (m, 8H, *m*-PhH), 4.45-4.50 (m, 6H, OCH_2), 4.37 (br, 6H, OCH_2), 4.30 (br, 6H, OCH_2), 4.11 (s, 3H, OCH_3), 4.02-4.06 (m, 6H, OCH_2), 3.74 (br, 12H, carborane-H),

1.30-1.60 (br, 51H, BH), -2.68 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 63 MHz) 160.3, 136.6, 135.5, 121.1, 114.2, 113.5, 73.4, 70.8, 69.8, 69.0, 60.9, 55.5, 47.7. HRMS (MALDI-TOF) *m*/*z* 1992.1954 (M - $3K^+$ + $3Na^+$ + H^+)$^+$, Calcd. for $C_{69}H_{117}B_{54}Co_3N_4Na_3O_{10}$ 1992.1899.

Synthesis of 12: The conjugate **12a** was prepared from 5,10,15-tris(4-hydroxyphenyl)-20-[4-(*tert*-butoxycarbonylmethyl)phenyl]porphyrin (see Chapter 1) and compound **2** as described above, and the corresponding *tert*-butyl protected conjugate **12a** was obtained in 91% yield, mp = 262-265 °C (dec). HPLC t_R = 12.52 min. UV-vis (acetone) λ_{max} (ε/(M^{-1} cm^{-1})) 419 (ε, 396 700), 516 (26 000), 552 (21 200), 593 (8600), 650 (9000). ^{1}H NMR (acetone-d_6, 250 MHz): δ 8.90-8.93 (m, 8H, β-H), 8.13 (d, 8H, J = 7.9 Hz, *o*-PhH), 7.36-7.43 (d, 8H, J = 8.5 Hz, *m*-PhH), 4.92 (s, 2H, CH_2), 4.50 (s, 6H, OCH_2), 4.33 (s, 6H, OCH_2), 4.28 (s, 6H, OCH_2), 4.04 (s, 6H, OCH_2), 3.75 (s, 12H, carborane-H), 1.6-3.0 (br, 51H, BH), 1.59 (s, 9H, CH_3), -2.70 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 63 MHz): δ168.5, 159.7, 158.9, 136.1, 135.5, 134.9, 131.8, 120.6, 120.2, 113.7, 82.1, 72.8, 70.2, 69.2, 68.5, 66.3, 65.8, 61.6, 54.8, 47.1, 28.1. LRMS (MALDI-TOF) *m*/*z* 2139.003 (M^+), Calcd. for $C_{74}H_{124}B_{54}Co_3K_3N_4O_{12}$ 2139.602. To a solution of this conjugate (100 mg, 0.0467 mmol) in chloroform (5 mL) was added TFA (5 mL) and the final mixture was stirred at room temperature for 4 h. The solvent was removed under vacuum and the residue was triturated with 5 mL of Et_2O. The resulting green precipitate was washed with Et_2O (6 × 10 mL) to remove residual TFA and dried under vacuum to give 93 mg, 95% yield, of pure conjugate **12**, mp = 283-285 °C (dec). UV-vis (acetone) λ_{max} (ε/M^{-1} cm^{-1})) 419 (ε, 408000), 516 (17800), 553 (14250), 593 (8300), 650 (8800). ^{1}H NMR (acetone-d_6, 250 MHz, TFA): δ8.78 (br, 8H, β-H), 8.48 (br, 8H, *o*-PhH), 7.64 (br, 8H, *m*-PhH), 5.10 (s, 2H, CH_2), 4.53 (s, 6H, OCH_2), 4.36 (s, 6H, OCH_2), 4.29 (s, 6H, OCH_2), 4.05-4.06 (m, 6H, OCH_2), 3.73 (s, 12H, carborane-H), 0.77-2.43 (br,

51H, BH). LRMS (MALDI-TOF) *m/z* 2083.518 $(M + H)^+$, Calcd. for $C_{70}H_{116}B_{54}Co_3K_3N_4O_{12}$ 2083.498. HPLC t_R = 16.59 min.

Synthesis of 14 and 15: 5-(4-Aminophenyl)-5,10,15-triphenylporphyrin 33.0 mg (0.05 mmol) and 41.0 mg (0.1 mmol) **2** were added to 2.5 mL $CHCl_3$ and 5 mL CH_3CN. The reaction mixture was refluxed overnight. It was then separated on a silica gel column using a mixture of chloroform and ethyl acetate for elution, giving two major fractions **14** and **15**. Recrystallization was performed from chloroform/hexane and then dried under vacuum. Compound **14**: 25.7 mg (0.024 mmol), yield 46 %. HRMALDI-TOF-MS for $C_{52}H_{59}B_{18}Co_2NaN_5O_2$: Calcd 1063.5794 $[M+H]^+$, found 1063.5802; Calcd 1039.5818 $[M-Na]^-$, found 1039.5863. ^{1}H-NMR (acetone-d_6, 250 MHz): 9.02 (d, 2H, β-H), 8.83 (m, 6H, β-H), 8.22 (m, 6H, o-phenyl-H), 7.95 (d, 2H, o-Ar-H), 7.81 (m, 9H, m,p-phenyl-H), 7.07(d, 2H, p-Ar-H), 5.23 (b, 1H, NH), 4.38 (s, 2H, OCH_2), 4.31 (s, 2H, OCH_2), 3.83 (t, 2H, OCH_2), 3.66 (m, 4H, car-H), 3.50 (t, 2H, NCH_2), 1.6-3.0 (br, 17H, BH), -2.67 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 63 MHz) 149.6, 142.9, 142.8, 136.4, 135.1, 130.3, 128.6, 127.6, 122.7, 120.7, 120.2, 111.8, 72.6, 70.2, 69.2, 55.3, 47.2, 44.2. UV-vis (acetone) λmax (nm) 415 (ε 242 200), 515 (15 900), 555 (11 600), 589 (6600), 651 (5600). HPLC (method b) t_R = 4.20.

Compound 15: 20.4 mg (0.014 mmol), yield 26%. HRMALDI-TOF-MS for $C_{60}H_{87}B_{36}Co_2Na_2N_5O_4$: Calcd 1498.8910 $[M+H]^+$, found 1496.9001; Calcd 1472.8933 $[M-Na]^-$, found 1472.8957. ^{1}H-NMR (acetone-d_6, 250 MHz): 9.08 (d, 2H, β-H), 8.84 (m, 6H, β-H), 8.23 (m, 6H, o-phenyl-H), 8.08 (d, 2H, o-Ar-H), 7.80 (m, 9H, m,p-phenyl-H), 7.26 (d, 2H, p-Ar-H), 4.42 (b, 4H, OCH_2), 4.30 (b, 8H, OCH_2), 3.90 (b, 8H, OCH_2), 3.70 (b, 8H, car-H), 1.6-3.0 (br, 34H, BH), -2.60 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 63 MHz) 148.6, 142.7, 136.5, 135.0, 134.9, 129.5, 128.4, 127.4, 122.6, 120.5, 120.0, 111.1, 72.7, 69.0, 68.9, 55.3, 51.6, 47.0. UV-vis

(acetone) λmax (nm) 413 (ε 222 600), 516 (15 800), 559 (13 000), 591 (7900), 651 (6300). HPLC t_R = 13.93. HPLC (method b) t_R = 5.29.

General Procedure for Syntheses of Porphyrin (17-21). Cobaltacarborane **2** and the 4-pyridylporphyrin were dissolved into a 1:1 (v/v) mixture of chloroform and acetonitrile. The reaction mixture was stirred at 60 ℃ under an argon atmosphere until the reaction was complete (monitored by TLC and ^{1}H-NMR). The reaction mixture was cooled to room temperature and the solvent was evaporated under vacuum. The residue was washed with diethyl ether (3 x 5 mL) and with methanol (3 x 5 mL). Finally, the product was dried overnight under vacuum to afford the targeted conjugate.

5-(4'-Cobaltacarboranylpyridyl)-10,15,20-triphenylporphyrin (17). 5-(4'-Pyridyl)-10,15,20-triphenylporphyrin (61.6 mg, 0.10 mmol) and compound **2** (61.5 mg, 0.15 mmol) were heated in 40 mL of chloroform/acetonitrile (1:1) for 12 h. The title conjugate was obtained in 98.4% yield (101.0 mg) as a purple solid. UV-Vis (acetone) λ_{max} (ε/$M^{-1}cm^{-1}$) 418 (ε, 157 600), 515 (10 100), 551 (5300), 590 (3400), 646 (2600). ^{1}H NMR (acetone-d_6, 250 MHz): δ 9.73 (d, 2H, J = 6.7 Hz, *o*-PyrH), 9.09 (m, 4H, β -H), 9.00 (d, 2H, J = 4.8 Hz, *m*-PyrH), 8.90 (s, 4H, β-H), 8.27 (m, 6H, *o*-PhH), 7.86 (m, 9H, *m, p*-PhH), 5.34 (t, 2H, NCH_2), 4.45 (t, 2H, OCH_2), 4.05 (t, 2H, OCH_2), 4.03 (t, 2H, OCH_2), 3.84 (s, 2H, carborane-H), 3.82 (s, 2H, carborane-H), 1.6-3.0 (br, 17H, BH), -2.74 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 250 MHz): δ 160.1, 144.8, 142.2, 135.1, 133.6, 128.9, 127.7, 123.0, 122.1, 113.3, 73.0, 69.7, 61.8, 52.5, 46.9. HRMS (MALDI-TOF) *m/z* 1026.5713, Calcd. for $C_{51}H_{58}B_{18}CoN_5O_2$ 1026.5739.

***Trans*-5,10-Bis(4'-cobaltacarboranylpyridyl)-15,20-diphenylporphyrin (18)**. *trans*-5,15-Di(4'-pyridyl)-10,20-diphenylporphyrin (16.0 mg, 0.026 mmol) and compound **2** (43 mg, 0.10 mmol) were heated in 40 mL of chloroform/acetonitrile 1:1 for 2 d, affording 34.1 mg (91.1%)

of the title conjugate . UV-Vis (acetone) λ_{max} (ε/$M^{-1}cm^{-1}$) 422 (ε, 129400), 516 (8,400), 554 (5,200), 590 (3,400), 651 (2,800). ^{1}H NMR (acetone-d_6, 250 MHz): δ 9.76 (d, 4H, *J* = 6.7 Hz, *o*-PyrH), 9.13 (m, 8H, β-H), 9.04 (d, 4H, *J* = 4.9 Hz, *m*-PyrH), 8.29 (m, 4H, *o*-PhH), 7.88 (m, 6H, *m,p*-PhH), 5.34 (t, 4H, NCH_2), 4.44 (t, 4H, OCH_2), 4.06 (s, 4H, OCH_2), 4.02 (s, 4H, OCH_2), 3.85 (m, 8H, carborane-H), 1.6-3.0 (br, 34H, BH), -2.80 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 250 MHz): δ 160.0, 145.3, 142.2, 135.5, 133.8, 129.5, 128.2, 123.2, 115.5, 73.7, 70.4, 62.6, 53.1, 47.6. HRMS (MALDI-TOF) *m/z* 1438.9027, Calcd. for $C_{58}H_{86}B_3Co_2N_6O_4$ 1438.8987.

***cis*-5,15-Bis(4'-cobaltacarboranylpyridyl)-10,20-diphenylporphyrin (19)**: *cis*-5,10-Di(4'-pyridyl)-15,20-diphenylporphyrin (16.0 mg, 0.026 mmol) and compound **2** (43 mg, 0.10 mmol) were heated in 40 mL of chloroform/acetonitrile (1:1) for 2 d, affording 33.5 mg (91.0 %) of the title conjugate. UV-Vis (acetone) λ_{max} (ε/$M^{-1}cm^{-1}$) 423 (ε, 141000), 518 (10600), 553 (5000), 590 (4000), 645 (1600). ^{1}H NMR (acetone-d_6, 250 MHz): δ 9.75 (d, 4H, J = 6.7 Hz, *o*-PyrH), 9.18 (s, 2H, *m*-PyrH), 9.11 (d, 6H, J = 6.7 Hz, β-H), 9.04 (d, 2H, J = 4.9 Hz, β-H), 8.92 (s, 2H, *m*-PyrH), 8.26 (m, 4H, *o*-PhH), 7.84 (m, 6H, *m*, *p*-PhH), 5.33 (t, 4H, NCH_2), 4.50 (t, 4H, OCH_2), 4.06 (t, 4H, OCH_2), 4.03 (t, 4H, OCH_2), 3.84 (m, 8H, carborane-H), 1.6-3.0 (br, 34H, BH), -2.75 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 63 MHz): δ 159.9, 145.3, 142.1, 135.4, 133.8, 129.4, 128.0, 124.2, 114.6, 73.6, 70.3, 70.2, 62.5, 53.0, 47.5. HRMS (MALDI-TOF) *m/z* 1438.8960, Calcd. for $C_{58}H_{86}B_{36}Co_2N_6O_4$ 1438.8987.

5,10,15-Tris(4'-cobaltacarboranylpyridyl)-20-phenylporphyrin (20): 5,10,15-Tris(4'-pyridyl)-20-phenylporphyrin (31.0 mg, 0.05 mmol) and compound **2** (100.3 mg, 0.24 mmol) were heated in 40 mL of chloroform/acetonitrile (1:1) for 2 d to afford 83 mg (90.0%) of the title conjugate. UV-Vis (acetone) λ_{max} (ε/$M^{-1}cm^{-1}$) 425 (ε, 168000), 516 (12600), 553 (5600), 591 (4300), 647 (1900). ^{1}H NMR (acetone-d_6, 250 MHz): δ 9.79 (m, 6H, *o*-PyrH), 9.21 (d, 6H, *m*-

PyrH), 9.13 (m, 6H, β-H), 9.07 (d, 2H, β-H), 8.29 (m, 2H, *o*-PhH), 7.91 (m, 3H, *m*, *p*-PhH), 5.34 (s, 6H, NCH_2), 4.43 (s, 6H, OCH_2), 4.04 (s, 6H, OCH_2), 3.99 (s, 6H, OCH_2), 3.84 (d, 12H, carborane-H), 1.6-3.0 (br, 51H, BH), -2.83 (s, 2H, NH). ^{13}C NMR (acetone-d_6, 63 MHz): δ 159.2, 145.2, 142.1, 135.2, 133.5, 129.4, 127.9, 124.2, 116.1, 73.4, 70.0, 62.3, 52.7, 47.3. HRMS (MALDI-TOF) *m/z* 1850.2320, Calcd. for $C_{65}H_{114}B_{54}Co_3N_7O_6$ 1850.2263.

***meso*-Tetrakis(*N*-cobaltacarboranylpyridinium-4-yl)porphyrin (21)**: 5,10,15,20-Tetrakis(4'-pyridyl)porphyrin (17.0 mg, 0.027 mmol) and compound **2** (62.0 mg, 0.15 mmol) were heated in 40 mL of chloroform/acetonitrile (1:1) for 3 d, affording 53.3 mg (87.7%) of the title conjugate. UV-Vis (acetone) λ_{max} ($\varepsilon/M^{-1}cm^{-1}$) 427 ($\varepsilon$, 210000), 517 (15600), 553 (5900), 590 (5600), 645 (1500). ^{1}H NMR (acetone-d_6, 250 MHz): δ 9.80 (d, 8H, J = 6.3 Hz, *o*-PyrH), 9.26 (s, 8H, β-H), 9.15 (d, 8H, J = 6.3 Hz, *m*-PyrH), 5.36 (s, 8H, NCH_2), 4.43 (s, 8H, OCH_2), 4.05 (s, 8H, OCH_2), 4.00 (s, 8H, OCH_2), 3.85 (d, 16H, carborane-H), 1.6-3.0 (br, 68H, BH), -2.89 (s, 2H, NH). ^{13}C-NMR (acetone-d_6, 250 MHz): δ 159.4, 145.9, 134.1, 117.4, 74.0, 70.6, 70.5, 62.9, 53.3, 47.9. HRMS (MALDI-TOF) *m/z* 2262.5566, Calcd. for $C_{72}H_{142}B_{72}Co_4N_8O_8$ 2262.5509.

***N*-Cobaltacarboranyl-5,10,15,20-tetraphenylporphyrin (22)**: H_2TPP (61.4 mg, 0.10 mmol) and [3,3'-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$(1',2'-$C_2B_9H_{10}$)] (65.4 mg, 0.16 mmol) were dissolved in ODCB (25 mL). The reaction solution was heated to 140 ℃ and the color changed to green in about 15 min. Two h later, TLC indicated no starting H_2TPP left and the reaction was stopped. The reaction mixture was directly loaded onto a silica gel column using toluene to elute the ODCB solvent and a trace of TPP. Then the title porphyrin was eluted using DCM and recrystallized from chloroform/hexane. After drying under vacuum, porphyrin **3** was obtained in 81% yield (82.8 mg), along with 4.7% (6.8 mg) of porphyrin **5**. For the title porphyrin, HRMALDI-TOF-MS for $C_{52}H_{59}B_{18}CoN_4O_2$: Calcd 1025.5788, found 1025.5717. ^{1}H-NMR

($CDCl_3$, 250 MHz): 9.32 (d, 2H, J = 5.0 Hz, β-H), 9.08 (d, 2H, J = 5.0 Hz, β-H), 8.85 (s, 2H, β-H), 8.54 (b, 4H, o-phenyl-H), 8.32 (d, 2H, J = 7.75, o-phenyl-H), 8.23 (d, 2H, J = 7.75, o-phenyl-H), 8.15 (s, 2H, β-H), 8.00 (m, 6H, m, p-phenyl-H), 7.87 (m, 6H, m, p-phenyl-H), 3.91 (s, 2H, car-H), 3.30 (s, 2H, car-H), 3.07 (m, 2H, OCH_2), 2.71 (m, 2H, OCH_2), 0.71 (m, 2H, OCH_2), 0.1-4.0 (br, 17H, BH), - 4.83 (m, 2H, NCH_2). UV-Vis (DCM) λmax (nm) 450 (ε 320500), 613 (13800), 669 (38300).

***N*-Cobaltacarboranyl-2,3,7,8,12,13,17,18-octaethylporphyrin (24)**: H_2OEP (**2**) (53.5 mg, 0.10 mmol) and [3,3'-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$(1',2'-$C_2B_9H_{10}$)] (43.3 mg, 0.11 mmol) were dissolved in 10 mL of ODCB. The reaction solution was stirred at 140 ℃ for 2 h until TLC indicated no H_2OEP was left. The reaction mixture was purified on a silica gel column using DCM/hexane for elution. The first purple fraction was collected and recrystallized from chloroform/hexane and dried under vacuum to yield the title porphyrin (86.1 mg, 89%). HRMALDI-TOF-MS for $C_{44}H_{75}B_{18}CoN_4NaO_2$: Calcd. 968.6934 $[M+Na]^+$, found 968.6957. ^{1}H-NMR ($CDCl_3$, 250 MHz): 10.67 (s, 2H, meso-H), 10.41 (d, 2H, meso-H), 4.28-4.42 (m, 8H, CH_2), 4.18-4.22 (m, 2H, car-H), 4.04-4.15 (m, 8H, CH_2), 3.59 (brs, 2H, car-H), 3.02-3.05 (m, 2H, OCH_2), 2.27-2.30 (m, 2H, OCH_2), 1.96-2.01 (m, 12H, CH_3), 1.47-1.53 (m, 12H, CH_3), 0.09-0.22 (m, 2H, OCH_2), 0.1-4.0 (br, 17H, BH), - 5.60--5.57 (m, 2H, NCH_2). UV-Vis (acetone) λmax (nm) 400 (ε 145500), 539 (9200), 562 (12400), 581 (10200).

***N,N*-Di(cobaltacarboranyl)-5,10,15,20-tetraphenylporphyrin (23)**: Mono-substituted porphyrin **3** (26.0 mg, 0.025 mmol), [3,3'-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$(1',2'-$C_2B_9H_{10}$)] (20.1 mg, 0.05 mmol) and K_2CO_3 (35 mg, 0.25 mmol) were stirred in ODCB (10 mL) and then the reaction mixture was heated to 140 ℃ until the disappearance of starting porphyrin **3** according to TLC monitoring. The reaction mixture was purified on a silica gel column using DCM/ethyl acetate

for elution. The main green fraction was collected and recrystallized from chloroform/hexane and dried under vacuum, to yield the title porphyrin **(**26.6 mg, 73%). HRMALDI-TOF-MS for $C_{60}H_{87}B_{36}Co_2N_4NaO_4$: Calcd. 1458.8903, found 1458.8850, Calcd. 1481.8801 $[M+Na]^+$, found 1481.8874; Calcd. 1435.9006 $[M-Na]^-$, found 1435.9014. ^{1}H-NMR (acetone-d_6, 250 MHz): δ 9.08 (d, 2H, J = 4.9 Hz, β-H), 8.89 (m, 4H, β-H), 8.63 (b, 2H, o-phenyl-H), 8.43 (m, 3H, m, p-phenyl-H), 8.28 (m, 2H, o-phenyl-H), 8.10 (m, 6H, m, p-phenyl-H), 8.01 (m, 3H, m, p-phenyl-H), 7.88 (d, 2H, J = 4.7, β-H), 7.68 (m, 2H, o-phenyl-H), 7.46 (m, 2H, o-phenyl-H), 4.24 (brs, 4H, car-H), 3.48 (brs, 4H, car-H), 2.93 (brs, 4H, OCH_2), 2.49 (brs, 2H, OCH_2), 2.43 (brs, 2H, OCH_2), 0.69 (brs, 4H, OCH_2), 0.1-4.0 (br, 34H, BH), -2.53 (s, 1H, NH), -4.16 (m, 2H, NCH_2), -5.71 (m, 2H, NCH_2). UV-Vis (DCM) λmax (nm) 465 (ε 285950), 696 (58250).

***N,N*-di(cobaltacarboranyl)-2,3,7,8,12,13,17,18-octaethylporphyrin (25)**: Mono-substituted porphyrin **4** (48.5 mg, 0.05 mmol), [3,3'-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$(1',2'-$C_2B_9H_{10}$)] (30.5 mg, 0.075 mmol) and $NaHCO_3$ (42.3 mg, 0.5 mmol) were stirred with 10 mL of ODCB and then the reaction mixture was heated at 140 ℃ until complete disappearance of porphyrin **4** based on TLC analysis. The reaction mixture was purified on a silica gel column using DCM/ethyl acetate for elution. The main fraction was collected and recrystallized from chloroform/hexane and dried under vacuum to yield the title porphyrin (26.6 mg, 73.0%). HRMALDI-TOF-MS for $C_{52}H_{103}B_{36}Co_4Na_2N_4O_2$: Calcd. 1401.0078 $[M+Na]^+$, found 1401.0092. ^{1}H-NMR (acetone-d_6, 250 MHz): 11.38 (s, 1H, meso-H), 11.33 (s, 2H, meso-H), 11.09 (s, 1H, meso-H), 3.93-4.36 (m, 16H, CH_2), 3.81 (brs, 4H, car-H), 3.38 (brs, 4H, car-H), 2.85 (m, 4H, OCH_2), 2.36 (brs, 4H, OCH_2), 1.85-1.88 (m, 12H, CH_3), 1.44-1.56 (m, 6H, CH_3), 1.27-1.42 (m, 6H, CH_3), 0.12 (brs, 4H, OCH_2), 0.1-4.0 (br, 34H, BH), - 5.41--5.35 (m, 2H, NCH_2), -6.44-6.38 (m, 2H, NCH_2). UV-Vis (Acetone) λmax (nm) 427 (ε 141500), 573 (9800), 617 (5300).

Molecular Structure. The crystal structure of porphyrin-cobaltacarborane **17** was determined, using data collected at T = 110 K with MoKα radiation on a Nonius KappaCCD diffractometer. Crystal data: $C_{51}H_{58}B_{18}CoN_5O_2$, triclinic space group P-1, a=6.941(5), b=10.982(7), c=35.48(3) Å, α=89.46(2), β=86.86(3), γ=75.03(4)˚ V=2609(3) $Å^3$, Z=2, R=0.125 ($F^2>2\sigma$), Rw=0.359 (all F^2) for 7181 unique data and 324 refined parameters. Due to the limited quality of the crystal, anisotropic refinement was not possible, except for the Co atom. Disorder was present in the chain connecting the porphyrin to the cobaltacarborane, and two atoms were modeled as pairs of half-populated sites. The N-H hydrogen atoms could not be located.

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26 Private commication, Dr. Shinji, Japan. **2007**.

CHAPTER 3. SYNTHESIZE AND CHARACTERIZATION OF CARBORANYL PORPHYRINS AND CHLORIN

3.1. Introduction

Carboranes, members of the class of boron clusters, are well known for their characteristic properties such as spherical geometry, remarkable thermal and chemical stability, and a very hydrophobic molecular surface. Carborane-containing organic functional groups are very useful molecules because they have wide applications in medicine[1-3] and materials areas[4-5]. Medical applications of the carboranes have been in the field of boron neutron capture therapy (BNCT) of cancer, utilizing the high boron content of the carborane. Recently, carboranes have also been used as a hydrophobic core for biologically active molecules because of their hydrophobic character and their spherical geometry[6].

We were interested in the synthesis of C-C linked carboranyl systems, which is commonly achieved by nucleophilic substitution using a carborane lithium complex or other metal complex[7]. Metal-catalyzed reactions of B-C bond formation have seen limited success[8-11]. C-C coupling between carborane lithium complex and aromatic iodo derivatives had also been developed[12-15]. The common route for the synthesis of C-C linked ortho-carborane derivatives involves the addition of alkynes to activated boranes $B_{10}H_{14}L_2$[16], which fails to generate carborane containing molecules when there is more than one methylene unit present between the cage carbon and donor atoms. A detailed reaction summary review of carboranes was published recently by Valliant et al[17]. Since currently available synthetic methods either have limited applications, require tedious total synthesis, or require harsh conditions that functional groups can not survive. On the other hand, the presence of these functional groups might generate exciting mechanic properties of the polymer and eventually “smart” materials. Thus the development of efficient

versatile synthetic methodology for building carborane-containing monopyrroles and monothiophenes are necessary.

We are interested in carborane-containing porphyrins as promising boron neutron capture therapy (BNCT) agents because this type of molecule has been shown to have selectivity for tumor cells, ability for delivering therapeutic boron concentration, and persistence within tumors[18]. In many of the porphyrin-carborane constructs under investigation, the carboranes are linked to the porphyrin through heteroatoms, which are potentially metabolically labile[18]. Our group has synthesized some C-C linked carboranyl porphyrins through total synthesis of carboranyl-aldehydes[19] or carboranyl-pyrroles[20]. Those compounds are very promising BNCT candidates. However, their synthetic routes are generally long, especially for unsymmetrical porphyrins. Efficient and regioselective brominations of pyrrole and tetra-arylporphyrins have been reported[21-25], and these make possible the selective modification of pyrrole and β-positions of porphyrin through metal-catalyzed cross-coupling reactions[26-30]. Among these, the Suzuki-coupling reaction[31] is suitable for introducing a variety of groups at the β-positions of porphyrin macrocycles by coupling halo-substituted porphyrins with the corresponding boronic acids or esters. Thus I decided to explore the possibility of efficiently synthesizing novel porphyrins using metal-catalyzed cross-coupling reactions. In the first part of this Chapter, porphyrins functionalized with carboranes at the meso or beta- positions were successfully synthesized via Suzuki coupling reactions[32].

In the second part of this Chapter, I report the synthesis of boronated porphyrins and chlorins via a one pot reaction. The carboranyl chlorin is currently being investigated as dual sensitizer for the boron neutron capture therapy (BNCT) and the photodynamic therapy (PDT) of cancer because it has strong long-wavelength absorption at around 650 nm. BNCT and PDT are both

binary therapies involving the selective accumulation of a sensitizer within tumor tissue, followed by irradiation of the tumor with neutrons (in BNCT) or with light (in PDT). Because it can be easy to deliver with minimal invasiveness, while leading to increased therapeutic effect due to the targeting of different mechanisms of tumor cell destruction, the combination of BNCT and PDT using a single drug has added advantages. The development of more tumor-selective sensitizers for both the BNCT and PDT treatment of brain tumors can potentially increase the effectiveness of these two localized modalities and their combination[33]. Ideal dual sensitizers should be: first, amphiphilic long wavelength-absorbing sensitizers of high boron content; second, able to accumulate in glioma cells and to be retain there for a considerable amount of time; third, have low dark toxicity, but become highly toxic upon activation by low energy neutrons and by red light to kill tumor cells. Chlorins containing high boron content are particularly promising for dual application in BNCT and PDT because of their stronger absorptions in the red region of the optical spectrum, where light penetration through tissue is considerably increased, compared with porphyrins.[34] Boron-containing tetrabenzoporphyrins[35] and phthalocyanines[36, 37] are also reported as promising dual sensitizers. Herein, we report all efficient one-pot reaction to synthesize a carboranyl-porphyrin and chlorin. Prelimary results show that chlorin is a very promising dual sensitizer for BNCT and PDT.

3.2. Synthesis of Carboranyl Porphyrins via Suzuki-Coupling Reaction

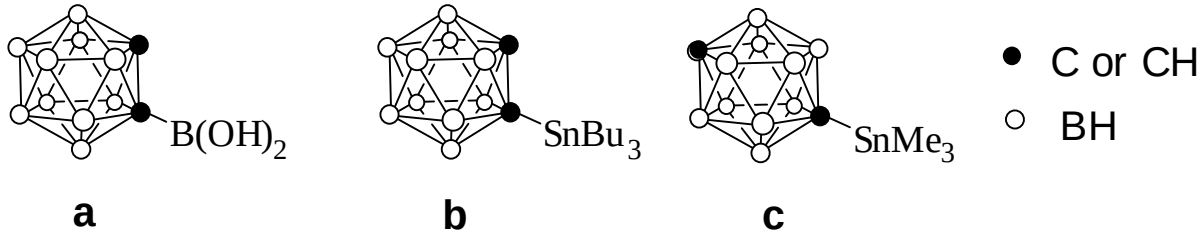
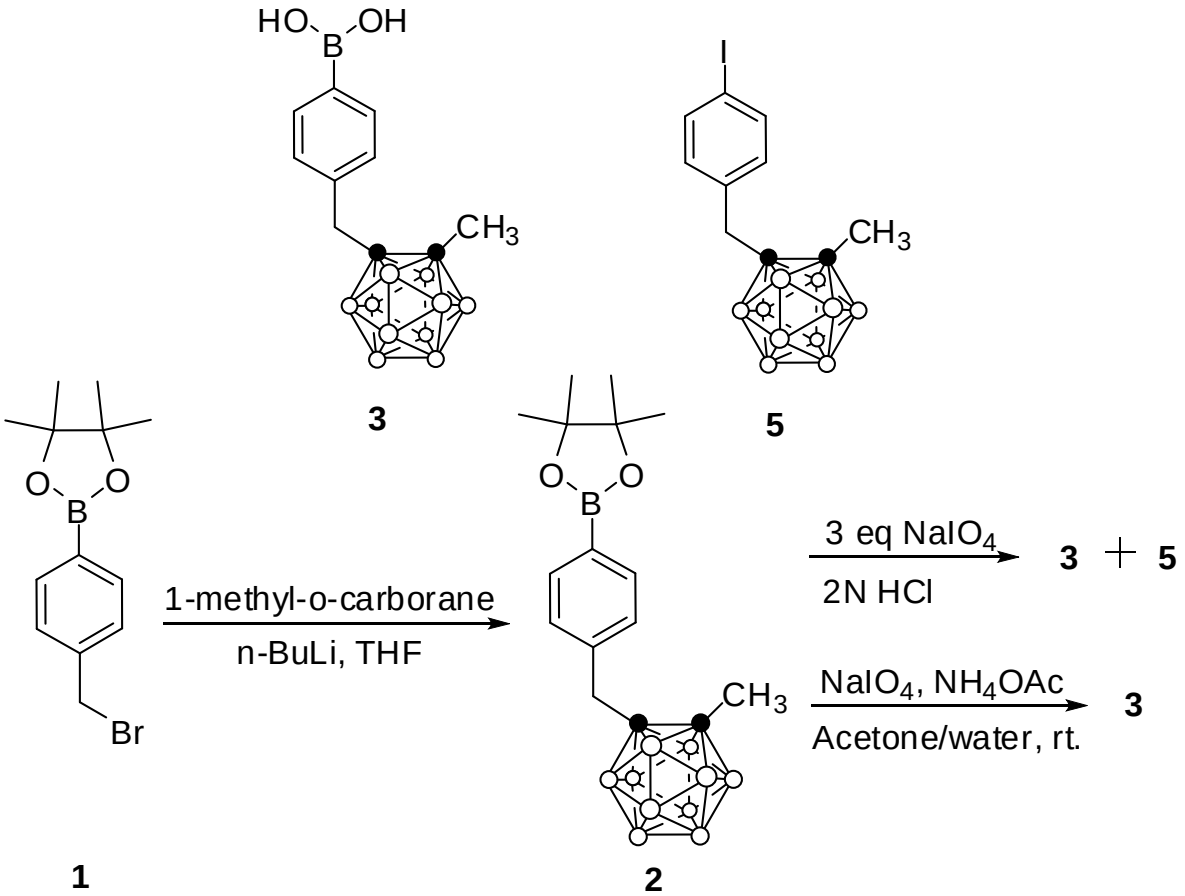


Figure 3-1: Chemical structure of metal-carborane derivatives involved in the coupling reaction.

The cross-couplings of organometallic reagents with organic halides or related electrophiles are usually catalyzed by transition metals. This type of coupling reaction provides an efficient way to generate new C-C bonds. Among those commonly used organometallic reagents, carborane lithium and carborane copper lithium complex, have limited applications due to the harsh reaction conditions associated with these reagents. For example, when carborane copper lithium complex was used as the organometallic reagent to covalently attach carborane to the meso-position of tetraphenylporphyrin, this reaction provided extremely low yield even after 12 days' refluxing in diglyme[38]. On the other hand, organic boronic acids are more attractive organometallic reagents readily available for the coupling reaction, and have been most widely used in the palladium catalyzed coupling reactions.



Scheme 3-1: Synthesis of the boronic acid **3.**

These organic boronic acids generally require mild reaction conditions for the coupling, which makes most of the common organic functional groups able to survive this reaction. We were initially interested in making a carboranyl-pyrrole, in which the carborane was directly attached to the pyrrole 3-position. To achieve this goal, I first needed to make either 1-carboranylboronic acid (**a** in *Figure 3-1*), or 1-carboranyl-metallic reagents (**b** and **c** in *Figure 3-1*), for the subsequent coupling reaction. The synthesis of the 1-carboranylboronic acid itself turns out to be problematic and mainly suffered from low yields. Meanwhile, although 1-carbonyltributyltin (**b**) has been used by Yamamoto's research group in reactions with aldehydes[39], a literature search indicated the limited application of these 1-carboranyl type metallic reagents in the palladium catalyzed coupling reaction. For example, it was reported by Michl et. al.[12] that 1-(trimethylstannyl)-*o*-carborane (**c**) failed to react with aryl iodides under palladium catalyzed condition. In this case, I decided to modify our approach by introducing a link between the carborane cage and the 3-position of the pyrrole ring. Compound **2** was synthesized by reacting commercial available compound **1** with 1-methyl-o-carborane. After deprotection with *n*-butyl lithium, compound **2** was obtained in 91% yield (*Scheme 3-1*). Oxidation of **2** using sodium periodate, followed by hydrolysis with 2N HCl aqueous solution provided **3** in 81% yield[40] (*Scheme 3-1*). However, the reliability of this process is poor. It was found that the yield of this reaction heavily depends on the acid concentration and the subsequent work-up process. In some cases, a very non-polar product was obtained from this procedure, instead of the desired polar acid. This non-polar product was originally assumed to be the corresponding boroxine trimer. The use of this compound in the subsequent Suzuki-coupling reaction was assumed to generate exclusively compound 4 as confirmed by X-ray structure (*Figure 3-2).*

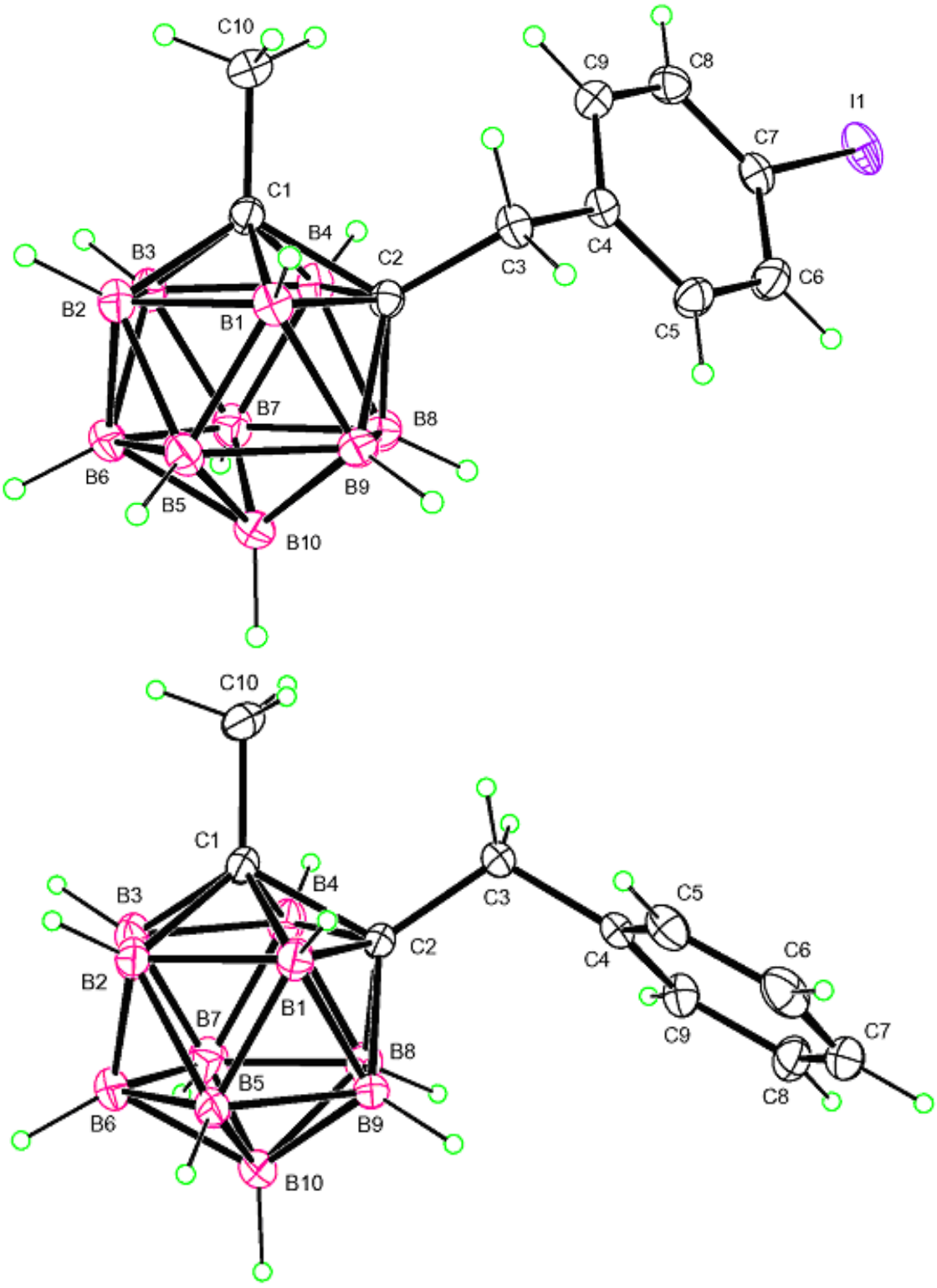


Figure 3-2: X-ray structures of **5** (left) and **4** (right).

However, the isolated product from this reaction surprise turned to be compound **5**, as confirmed from NMR and X-ray structure. The spectroscopy results are in agreement with the structure identification results. The structure of the new aryl iodide 5 was confirmed by X-ray crystallography (Figure 3-2). The C-I distance is 2.0967(18) Å, and the iodobenzyl substituent is oriented essentially *anti* to a B of the carborane. Torsion angle B1-C2-C3-C4 is -172.79(15)°, and torsion angle C1-C2-C3-C4 is -103.65(18)°. Although the underlying mechanism for the formation of compound 5 under this circumstances is still unclear, fortunately we were still able to generate a reliable procedure to produce the desired boronic acid in high yield by simply using ammonium acetate[41] to substitute the acid in the work-up step.

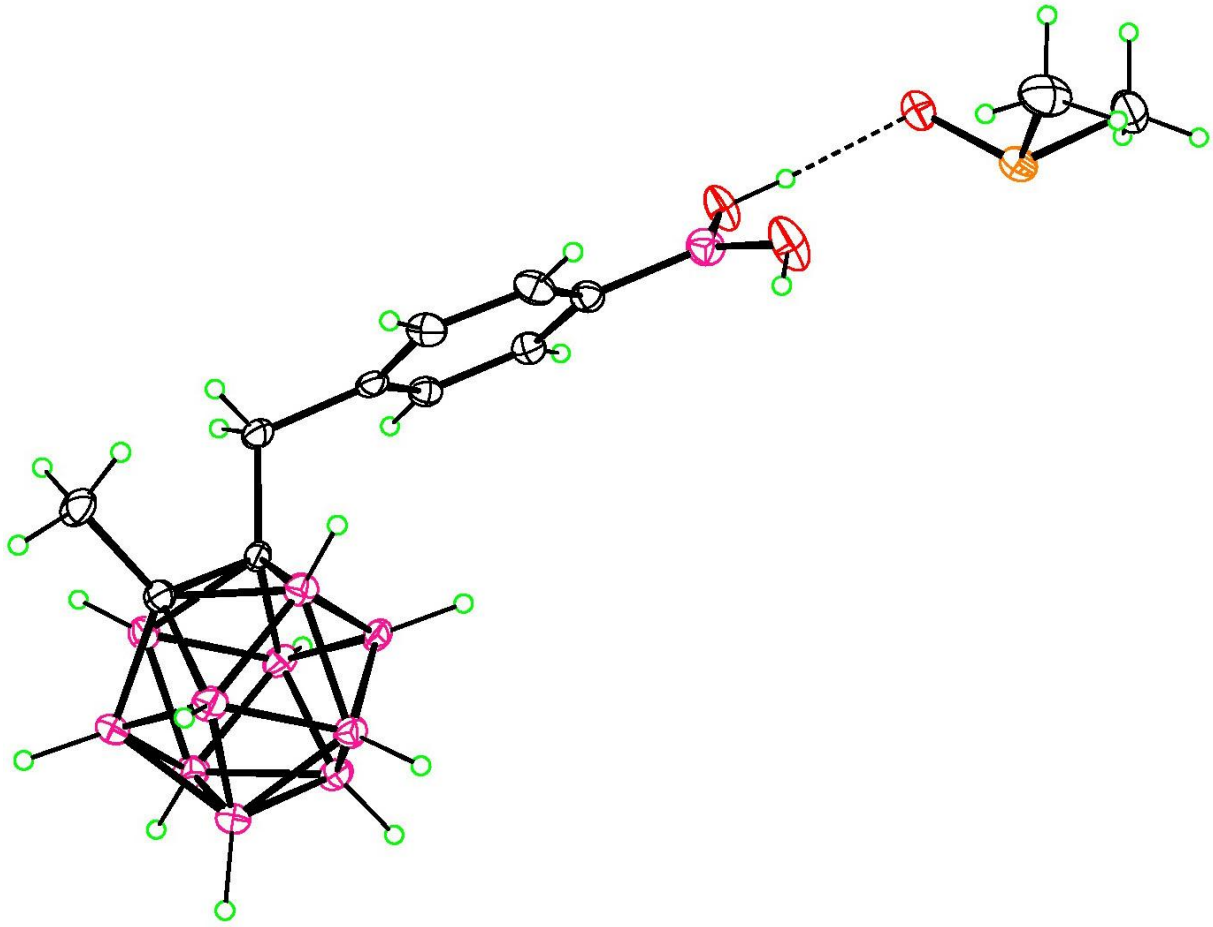
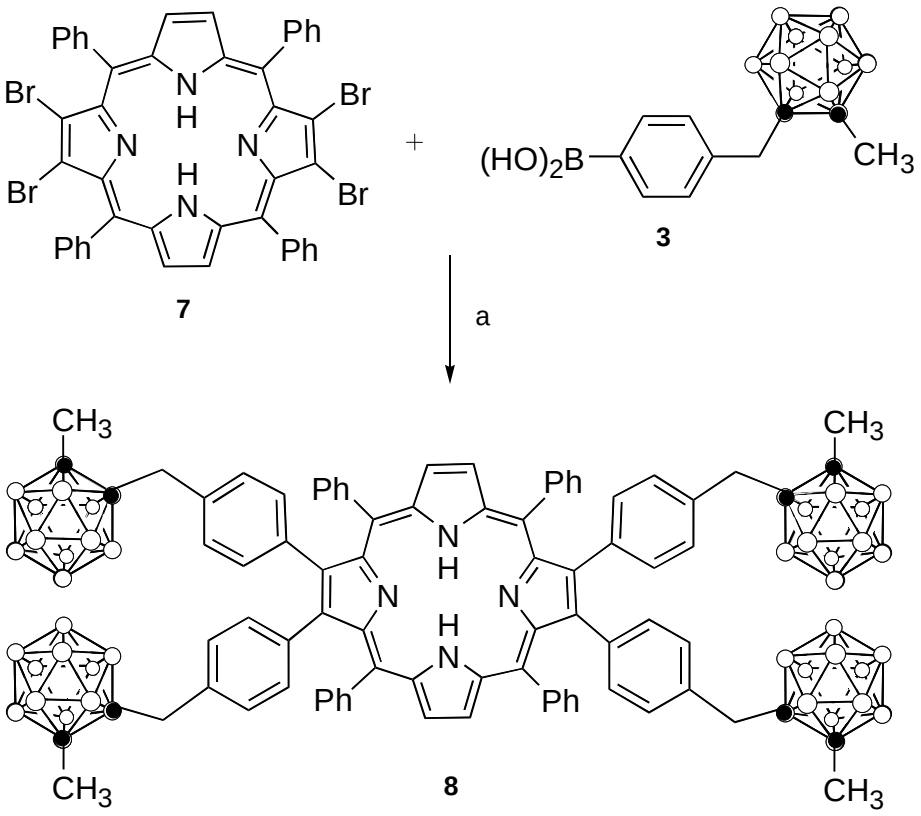


Figure 3-3: Molecular structure of boronic acid **3**.



Scheme 3-2: Reaction conditions: a) $Pd(PPh_3)_4$, toluene, K_2CO_3, 78%.

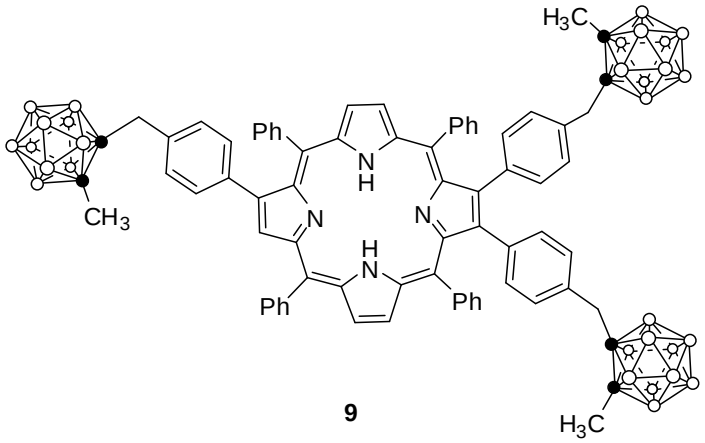


Figure 3-3 shows the structure of carboranyl boronic acid **3**. The $B(OH)_2$ moiety is twisted out of the phenyl plane by 33.5(2)° and has the expected conformation, in which one OH group is oriented *syn*, and the other *anti*. The compound crystallizes as the 1:1 solvate with DMSO, and

both OH groups form near-linear hydrogen bonds with DMSO oxygen (O…O 2.739(2) and 2.823(2) Å), one of which is shown in *Figure 3-3*.

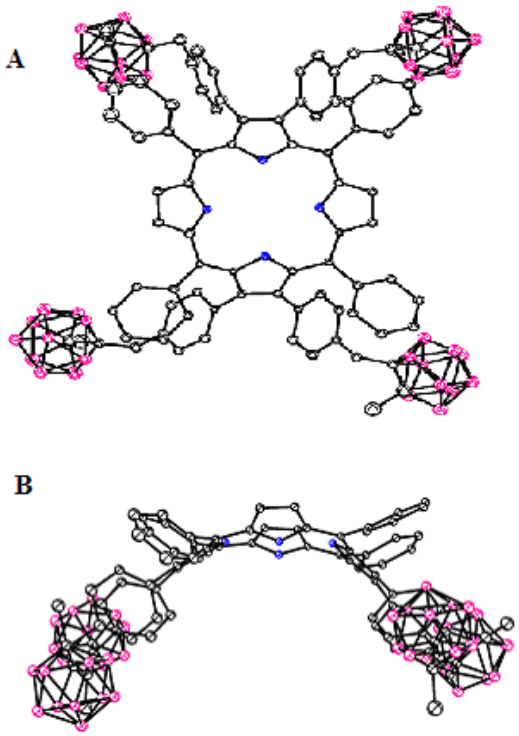
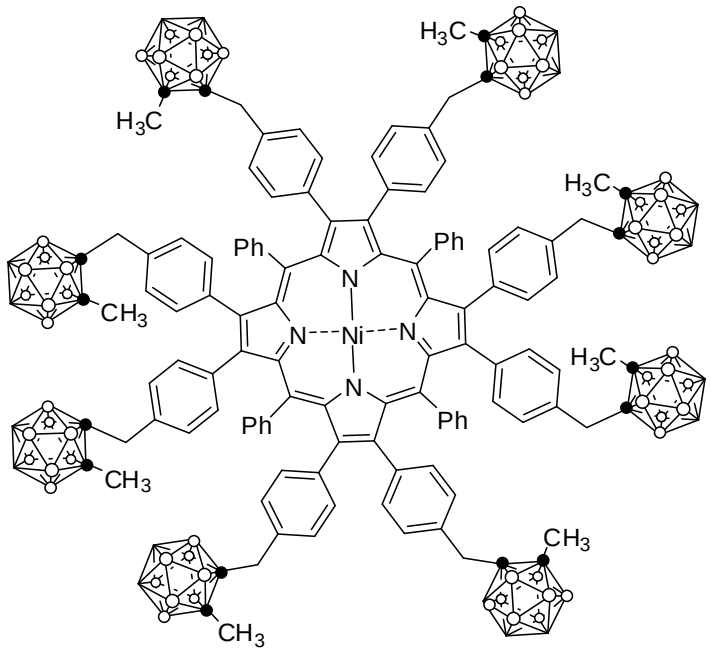


Fig 3-4. X-Ray structure of porphyrin **8**. A) From the top; B) end-on view showing saddled conformation. Hydrogen atoms are omitted for clarity.



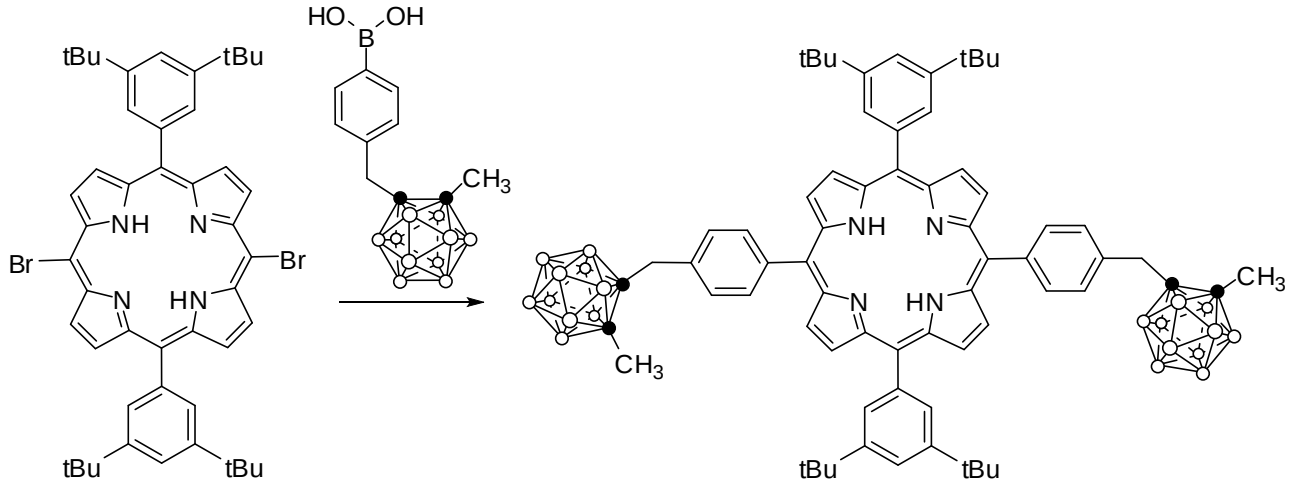
10

The tetrabromo porphyrin **7** was synthesized in refluxing chloform using tetraphenyl porphyrin **6** and 6 equivents of NBS according to literature[23]. The Suzuki coupling reaction of bromo-porphyrin **7** with boronic ester **2** was investigated because it would generate novel β-substituted carboranyl porphyrins which are hard to synthesize through total synthesis. First, I tried the reaction of **7** with **2** using the most common conditions: K_2CO_3 as the base and toluene as the solvent. The reaction gave many debrominated byproducts as confirmed by MALDI- TOF. Using THF/Water and Na_2CO_3 gave similar results but finished in shorter reaction time. Two major more polar fractions of the reaction mixture on silica gel were collected and characterized as porphyrin **8** and **9**. Both of them constantly gave about 15% yield by eluting through silica gel column using CH_2Cl_2. Dehalogenation is a common occurence in metal-catalyzed cross-coupling reactions, particularly when there is steric hindrance in the starting material. A similar debrominated product was recently reported from the reaction of 1,6,7,12-tetrabromoperylene bis-imide with phenylboronic acid under Suzuki coupling conditions.[42] The low yields of the reaction may be due to two reasons: first, the lower reactivity of boronic ester compared with boronic acid in the Suzuki reaction; second, the provided steric hindrance and crowding at the β-positions of the porphyrin. To solve this problem, I decided to use boronic acid **3**, thus we improved the reactivity while also reducing the steric hindrance of the transition state during the Suzuki coupling. As expected, the Suzuki coupling reaction of **7** with **3** resulted in a much cleaner reaction (Scheme 3-2), giving tetrasubstituted porphyrin **8** in 78% yield as well as 14% of porphyrin **9.** Porphyrin **9**, although as an unexpcted product, is a rare example of tri-β-substituted porphyrin. The ^{1}H-NMR spectra of **9** shows great degree of asymmetry. Crystals of the porphyrin **8**, as the dicationic bis-trifluoroacetate salt, were grown from dichloromethane–methanol. The structure of the dication is shown in Figure 3-3. It has a saddle conformation, with

the N–H groups pointing alternately up and down. Opposite pyrrole planes form dihedral angles of 67.5(2) and 69.7(2) °, while adjacent pyrrole planes form smaller dihedral angles, in the range 41.7(2)–51.7(2) °. This conformation allows the four N–H hydrogen atoms to avoid unfavorable contacts in the center of the porphyrin ring, and to form hydrogen bonds to trifluoroacetate anions, one above the porphyrin and one below. The N···O distances in these four hydrogen bonds are in the range 2.733(9)–2.848(8) Å.

Similarly, the Ni-β-octabromo-tetraphenylporphyrin NiTPP (prepared according to literature[24], and excess NBS in refluxing ODCB) was successfully coupled with excess boronic acid **3** to give porphyrin **10** in 18 % yield after purification by preparative TLC. However, coupling of the free-base β-octabromo-tetraphenyl porphyrin with boronic acid 3 failed to give the target compound. The Ni(II)–porphyrin 10 gave a molecular ion peak at 2643.8 by MALDI-TOF MS and characteristic ^{1}H-NMR signals consistent with those previously reported for β-octasubstituted porphyrins.[43] The UV-vis spectra of carboranylporphyrins **8**, **9** and **10** show, as expected, red-shifted Soret and Q bands compared with *meso*-tetraphenylporphyrin, thus reflecting the distortion from planarity of the peripherally substituted porphyrin rings.

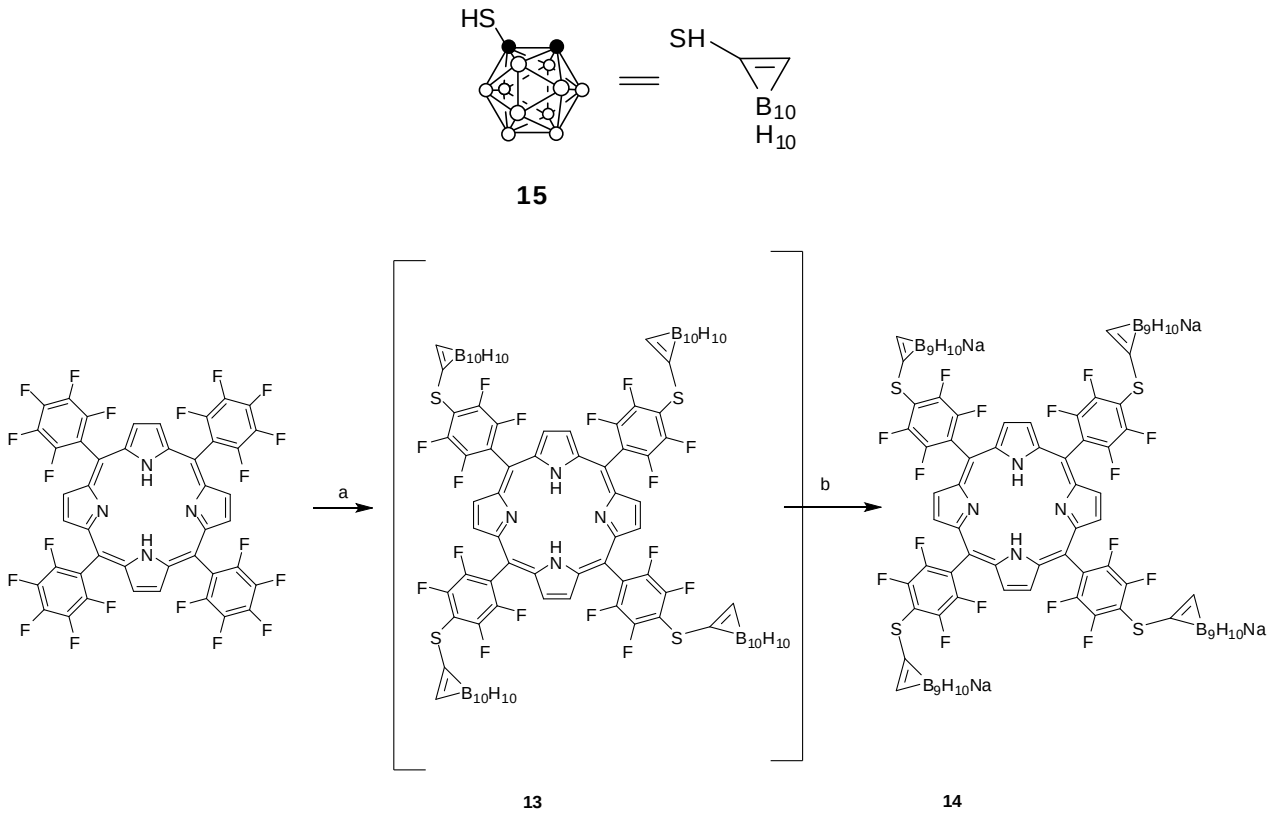
In addition, to test the viabilities of this coupling reaction, meso-subsituted porphyrin 11 was also prepared in high yield. The starting porphyrin **12** was prepared in four steps in according to the literature[44]: condensation between dipyrromethane and 3,5-diterbutyl benzaldehyde, metal insertion using $Zn(OAc)_2$ and bromination using two equiv of NBS, followed removal of Zn by using TFA. The porphyrin 11 was then synthesized through Suzuki coupling in 87 % yield from bromo porphyrins 12 (*Scheme 3-3*).



Scheme 3-3: Reaction conditions: $Pd(PPh_3)_4$, toluene, K_2CO_3.

3.3. Synthesis of Carboranyl Porphyrins and Chlorin

In view of the significant need for rapid synthesis of porphyrin derivatives, especially for therapeutic applications, I developed methods for the facile preparation of carboranylporphyrin derivatives around a core platform of 5,10,15,20-tetrakis(2,3,4,5,6-pentafluorophenyl)porphyrin ($TPPF_{20}$). As a demonstration of the method, a carboranylporphyrin and a carboranyl-chlorin are grafted onto the core for evaluation as BNCT and PDT agents. $TPPF_{20}$ which is commercially available and can be routinely made in large quantities either by the Adler[45] or Lindsey[46] methods was selected for several reasons: first, the para-phenyl fluoro group is known to be reactive toward nucleophilic substitution reactions[47]; second, it is readily available and can be easily functionalized through the beta-positions to form chlorin and other reduced porphyrins[48]; third, $TPPF_{20}$ derivatives are readily available fluorinated photosensitizers, which can be studied by in vivo spectroscopy and imaging and also fluorinated porphyrin derivatives have been shown higher activities than non- fluorinated compounds[49].



Scheme 3-4: a) DMF, 15, K_2CO_3; b) KF.

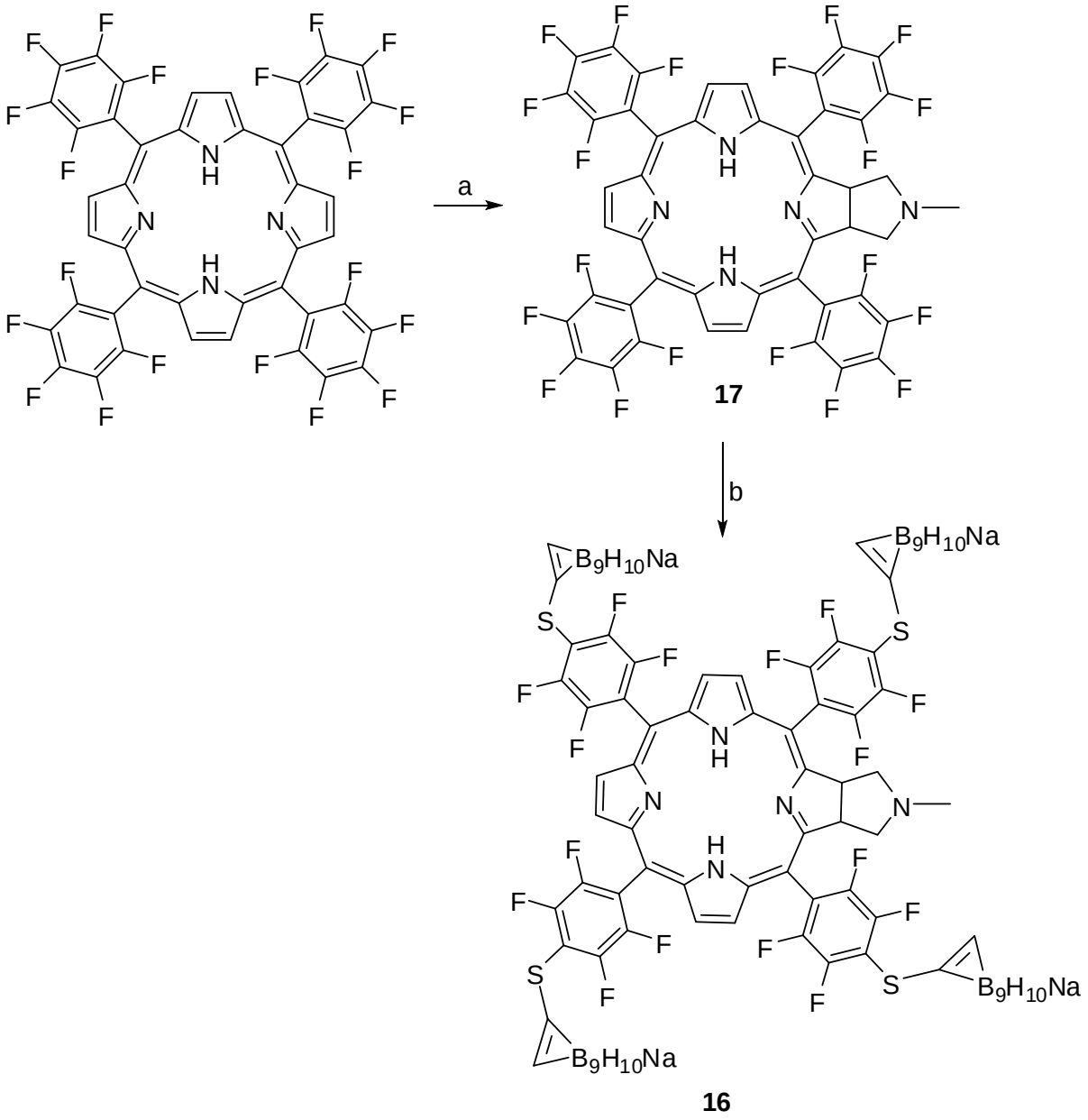
Fluorine-19 (19F) NMR is a technique with significant potential because of the relatively high sensitivity and low endogenous background. Due in part to its high MR sensitivity, fluorine has received considerable attention as an MR nucleus. Fluorine-19 MR has been used to study metabolism, tumor growth, and blood flow[50]. More recently, in vivo 19F MR has been used to measure tumor integrity and vasculature in subcutaneously implanted tumors in rats[51]. MR of fluorinated compounds is particularly attractive for in vivo studies of human and animal models. The 19F isotope has a 100% natural abundance, a spin of 1/2, and a MR sensitivity that is 83% that of hydrogen[52].

Previously reported TPPF20 derivatives were typically synthesized in refluxing DMF with a large excess of the amine or thiol reagents[47]. However, the yields were relatively poor, and the substitution was sometimes incomplete. It was found that better yields (around 90%), were

obtained by using thiol reagents and let it stir for a period of 12 h at room temperature in DMF with the presence of a stoichiometric amount of dialkylamine. Recently, Drain`s group also reported a efficient method by microwave heating enhanced reaction[53].

Here, we choose sulfur over oxygen since sulfur is known to be able to increase the stability of the resulted conjugate by avoiding reactions such as acid hydrolysis. Also sulfur is a weaker Lewis base compared to that of oxygen, which means it has a lower affinity for protons. Thus sulfur is hard to form the conjugated acid, which would be required for the hydrolysis of transition state.

Compound **15** was used as the nucleophilic reagent not only because it is easily available but also because it has sufficient nucleophilic ability. By simply mixing 10 equivalents of compound **15**, 1 equivalent of TPPF20 and 10 equivalent of K_2CO_3 in DMF at room temperature and let it stir for a period of two days, we expected to obtain compound **13** (*Scheme 3-4*). However, TLC indicated some very polar format porphyrins had formed instead of the expected nonpolar compound **13**, which suggested that the carborane cages may not be stable under the reaction conditions and readily undergoes degradation to form the nido cages. This degradation was not surprising under the condition for ortho-carboranes, especially for the sulfur group attached carboranes. It was previously found that a sugar modified carborane can be degraded to reaction and heated at 60 ℃ for two hours. Workup of the reaction by partion between ethyl acetate and water gave a solid residue (trace amount of DMF was removed by co-distillation with toluene). The residue was purified by silica gel column using ethyl acetate and acetone (1: 1) for eluting, giving the target porphyrin in 62 % yield of the nido form in water. Thus I decided to add some KF salt to make sure that all the carboranes are in the nido form in the product. The KF salt was added to the reaction mixture at the end of the reaction.



Scheme 3-5: a) toluene, $(CH_2O)n$, CH_3NHCH_2COOH; b) DMF, 15, K_2CO_3, then KF.

Next, taking advantage of the well-known 1,3-dipolar reaction of TPPF20, I was able to obtain the corresponding green chlorin **17** in one step with more than 60 % yield. There were also some minor product was isolated, which was confirmed to be the purple colored isobacteriochlorin. The chlorin was used to prepare carboranyl-chlorin **16** in 69% yield by using the same method as that for the preparation of **15**. The target carboranyl chlorin is particular

interesting because it has a characteric strong absorption around 650 nm, which is critical for PDT, and also it is unsymmetrical compound. The method presented here is the first reported method to be able to modify chlorin **17** to generate a novel soluble chlorin sensitizer **16**. Both **14** and **16** were fully characterized by NMR, HRMS and HPLC. The UV-vis of **14** is similar to the parent porphyrin, giving a Soret band at 413 nm and several Q bands (506 nm, 583 nm and 650 nm). Porphyrin **16**, as expected, showed characteristic chlorin absorption, giving a strong absorption at 650 nm as shown in *Figure 3-5*. HRMS (ESI) of compounds **14** and **16** showed well-matched isotope patterns with the calculated ones (*Figure 3-6*).

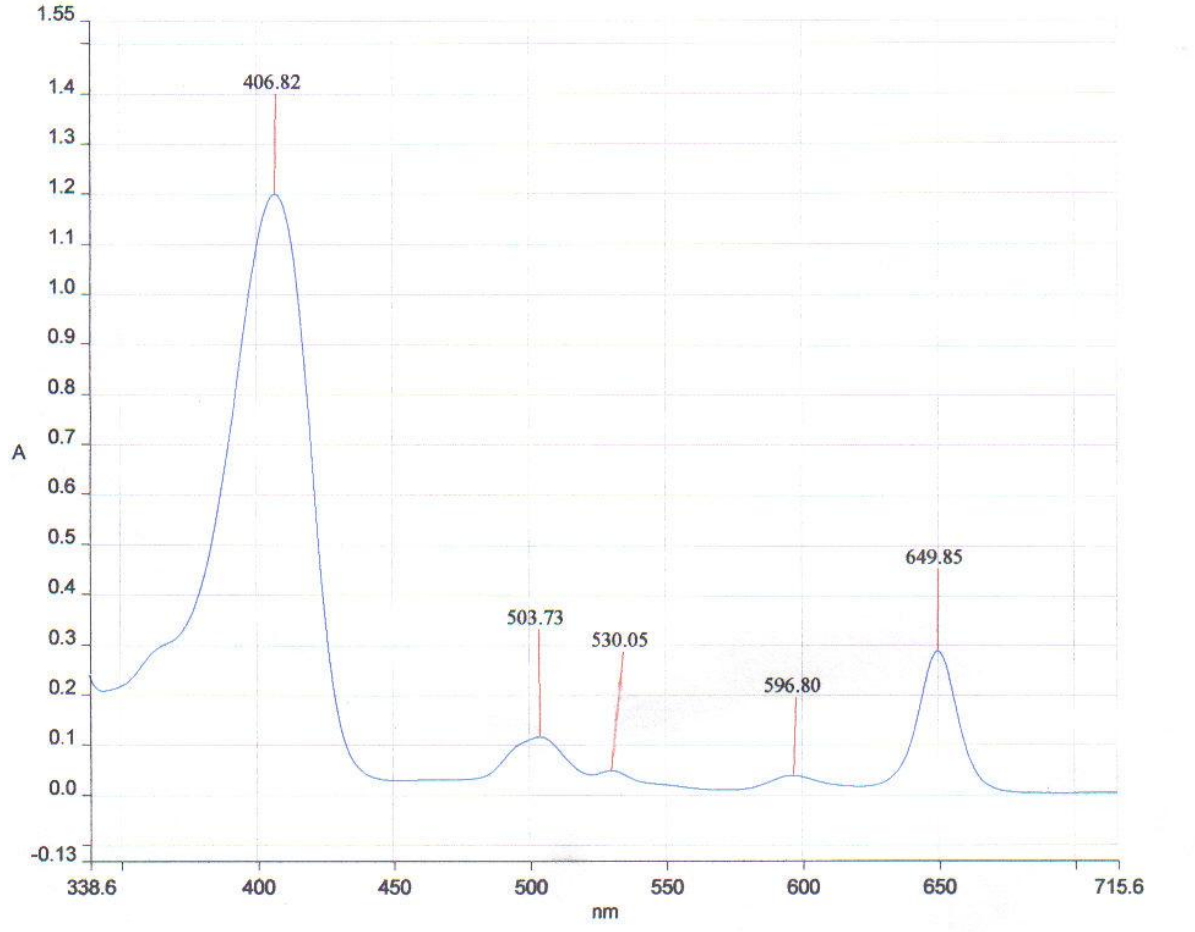


Figure 3-5: Absorption spectra of **16** in DMSO solution.

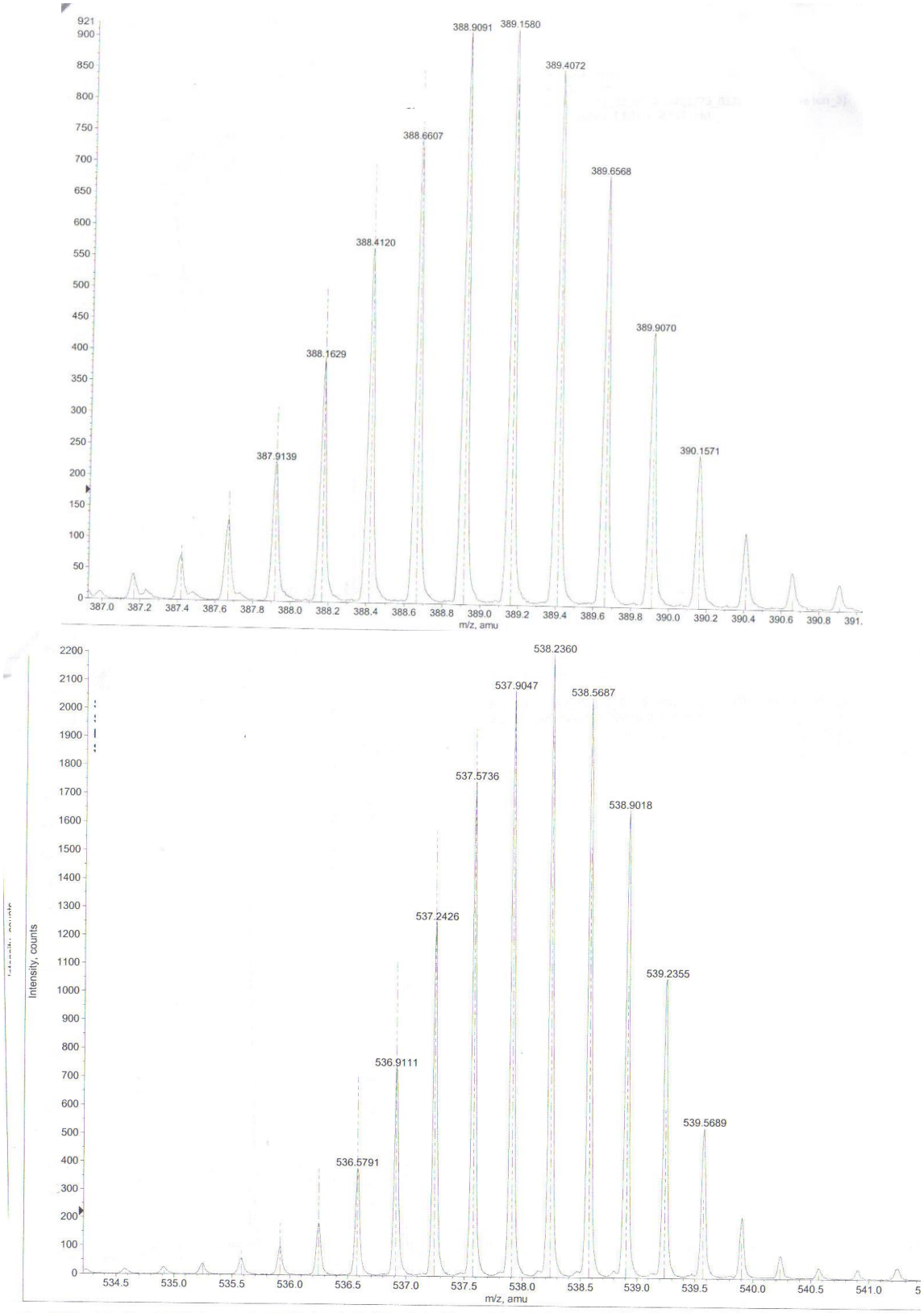
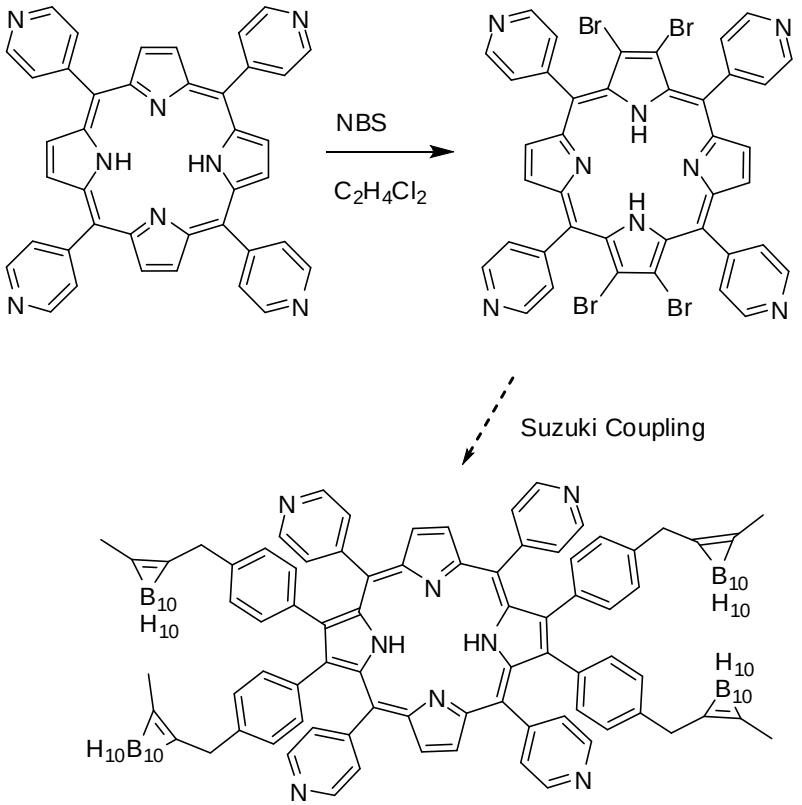


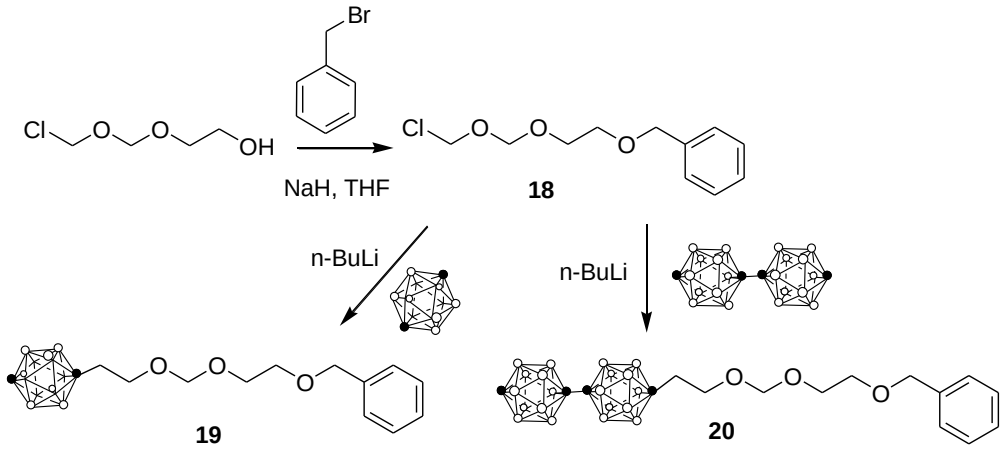
Figure 3-6: Exact mass of compound **14** (top, four charges species) and **16** (bottom, three charge species); Obtained value (solid line); Calculated value (dot line).

3.4. Several Attempted Approaches to Carboranyl-Porphyrins

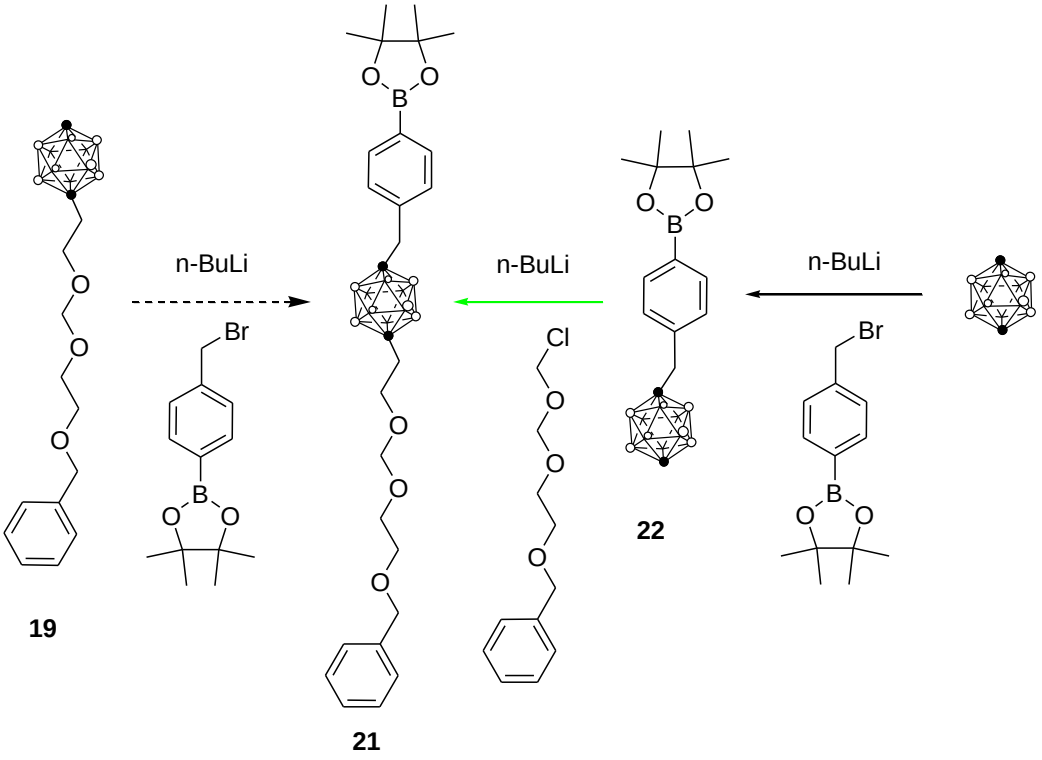
We are interested in building some carboranyl porphyrins containing positive charges or ethylene glycol water soluble groups because positive charges and neutral water soluble porphyrins may be taken up by cells in higher amount. However, some of the reactions were not successful and some approaches have not yet been finished. Two general approaches are investigated to expand our Suzuki coupling reactions: first, as shown in *Scheme 3-6*, tetrabromination of tetrapyridiumporphyrin was successful although in lower yield (40 %) than tetrabromination of H_2TPP. However, Suzuki coupling under the same conditions for porphyrin **7** was not successful, giving mainly debromination producs. Then I turned my attention to the synthesis of boronic acid carboranes containing positive charges or ethylene glycol groups. Thus compounds **19** and **20** were synthesized in two steps each in moderate yields (around 50 %) as shown in *Scheme 3-7*.



Scheme 3-6: Attempted synthesis of pyridium containing carboranyl porphyrins.



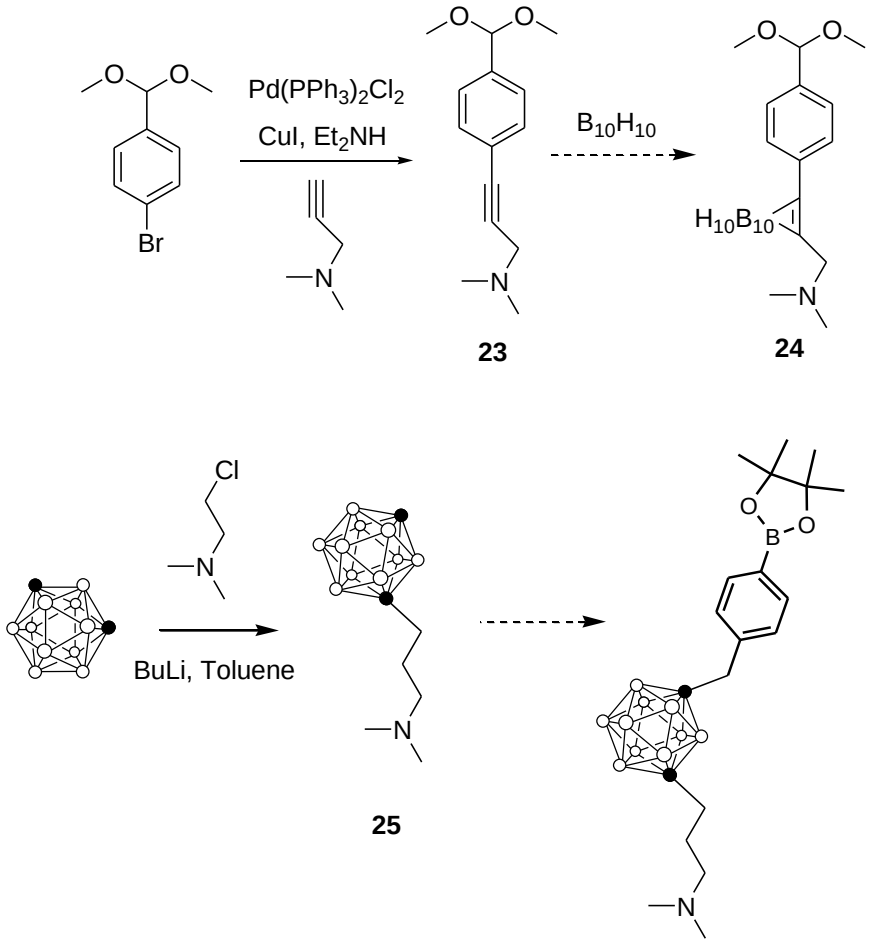
Scheme 3-7: Syntheses of compounds **19** and **20**.



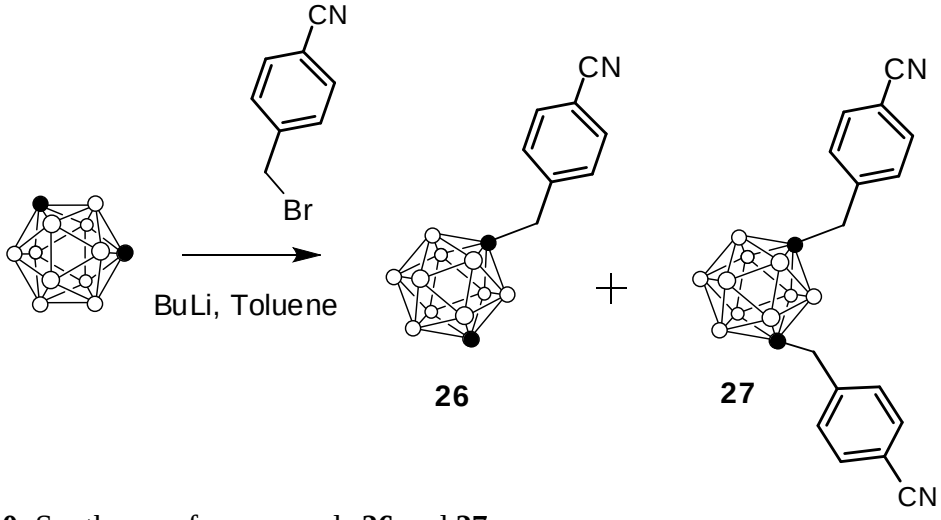
Scheme 3-8: Attempted synthesis of compound **21**.

However, further deprotonation with BuLi and reaction with RBr (*Scheme 3-8*) did not generate synthetic useful yield, although different RBr or RI and different base (tBuLi) were tried. Attempts to dimerization of **19** and **20** using BuLi and CuCl were also not successful. In an alternate approach, compound **22** (synthesized in 41 % yield from carborane) may produce **21** (*Scheme 3-8*). As shown in *Scheme 3-9*, although Sogayashi coupling to synthesize compound 23

was successful (78 % yield in 5 g scale), the following carborane formation gave a very low yield. Compound **25** was synthesized in 47 % yield and further function is still under way.



Scheme 3-9: Attempted synthesis of amino-containing compounds.



Scheme 3-10: Syntheses of compounds **26** and **27**.

Compounds **26** and **27** were obtained in similar method as described above and further functionalization can be achieved by conversion CN group into aldehyde will be possible. The X-ray structure of compound **27** is shown in *Figure 3-7*.

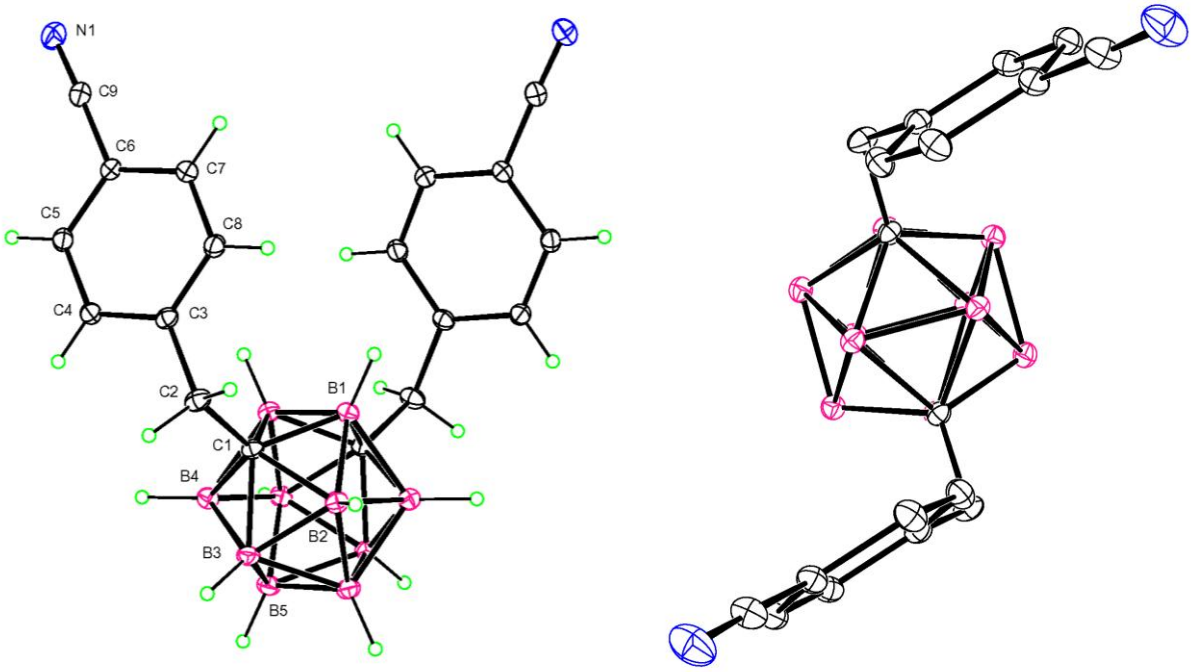


Fig 3-7: X-Ray structure **27** from different views.

3.5. Conclusions

In summary, I have successfully developed a new efficient route for the synthesis of a series of novel carboranyl-porphyrins under Suzuki couplings on either β or meso positions of porphyrins. Furthermore, an efficient one-pot synthesis of a carboranylporphyrin and a carboranylchlorin was achieved. Future work on the biological evaluation of the carboranylporphyrins is under way in our lab and by collaborative labs. Prelimary data show very promising results for chlorin **16** as both BNCT and PDT dual sensitizers.

3.6. Experimental

All reactions were monitored by TLC using 0.25 mm silica gel plates with or without UV indicator (60F-254). Carborane was detected by emerging into $PdCl_2$ in aqueous HCl solution (1 g $PdCl_2$ in 80 ml water and 20 ml concentrated HCl solution) and heated to see black spot on TLC. Silica gel Sorbent Technologies 32-63 μm was used for flash column chromatography. ^{1}H- and ^{13}C-NMR were obtained on either a DPX-250 or an ARX-300 Bruker spectrometer. Chemical shifts (δ) are given in ppm relative to $CDCl_3$ (7.26 ppm, ^{1}H), or CD_2Cl_2 (5.32 ppm, ^{1}H) unless otherwise indicated. Electronic absorption spectra were measured on a Perkin Elmer Lambda 35 UV-Vis spectrophotometer. MALDI-TOF mass spectra were obtained on an Applied Biosystems QSTAR XL, using positive method with dithranol as matrix unless otherwise indicated. Exact mass was obtained from ESI-TOF under negative or positive mode. The isotope peaks were matched with calculated patterns. Only the most abundant peaks are listed below (see the copy of spectra for isotope peaks).Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

Compound 2: 1-Methyl-o-carborane (530 mg, 3.35 mmol) was dissolved in 15 mL dry THF in a 100 mL Schlenk reaction tube equipped with magnetic stirring and cooled to 0 °C with an ice bath. 1.48 mL *n*-Butyllithium solution (3.69 mmol, 2.5 M solution in hexane) was added dropwise to the cooled solution. The solution was warmed to room temperature and stirred for 1 h. Then the solution was cooled to -78 °C. Compound **1** (1.00 g, 3.35 mmol) was dissolved into 5 mL dry THF and was added dropwise to the solution at -78 °C. Then the final reaction mixture was warmed to room temperature and was stirred overnight until TLC indicated no starting materials left. The reaction then poured into 50 mL brine and extracted by ethyl acetate (3 × 50 mL), dried over Na_2SO_4, and purified by column chromatography on silica gel, using 50 %

methlene chloride: 50 % hexane for elution. The title compound was obtained as a white power (1. 15 g) in 91 % yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.85 (2H, d, J = 7.76 Hz), 7.23 (2H, d, J = 7.81 Hz), 3.49 (2H, s), 2.19 (3H, s), 1.5-3.5 (10H, br), 1.41 (12H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.5, 136.6, 131.3, 85.6, 79.0, 78.3, 42.9, 26.5, 25.3. HRMS (ESI) $[M\text{-}C_2H(CH_3)_4]^-$: 291.2535, Calcd. for $C_{10}H_{20}B_{11}O_2$: 291.2565.

Compound 3: To a mixture of compound **2** (187 mg, 0.50 mmol), $NaIO_4$ (321 mg, 1.5 mmol) and NH_4Ac (116 mg, 1.5 mmol) were added 15 mL acetone and 5 ml water. The reaction mixture was stirred under air overnight until TLC indicated no starting boronic ester left. The reaction mixture was poured into 25 mL water and extracted by ethyl acetate (3 × 30 mL). The organic layer was dried over Na_2SO_4, concentrated and washed with hexane. Dried under vacuum and gave the title compound as a white power (130.1 mg) in 89 % yield. ^{1}H-NMR (300 MHz, DMSO-d^6) δ 8.06 (2H, s), 7.74 (2H, d, J = 7.75), 7.21 (2H, d, J = 7.86), 3.32 (2H, s), 2.21 (3H, s), 1.5-3.5 (10H, br). ^{13}C-NMR (75 MHz, DMSO-d^6) δ 137.2, 134.1, 129.5, 78.9, 76.4, 75.2, 40.5, 22.9. HRMS (ESI) $[M\text{-}H]^-$: 291.2566, Calcd. for $C_{10}H_{20}B_{11}O_2$: 291.2565.

Compound 5: 1-Methyl-*o*-carborane (325 mg, 2.05 mmol) was dissolved in 15 mL dry THF in a 100 mL Schlenk reaction tube equipped with magnetic stirring and cooled to 0 °C with an ice bath. 1.00 mL *n*-Butyllithium solution (2.50 mmol, 2.5 M solution in hexane) was added dropwise to the cooled solution. The solution was warmed to room temperature and stirred for 1 h. Then the solution was cooled to -78 °C. Compound **9** (606 m g, 2.05 mmol) was dissolved into 5 mL dry THF and was added dropwise to the solution at -78 °C. Then the final reaction mixture was warmed to room temperature and was stirred overnight until TLC indicated no starting materials left. The reaction then poured into 50 mL brine and extracted by ethyl acetate (3 × 50 mL), dried over Na_2SO_4, and purified by column chromatography on silica gel, using

15 % ethyl acetate: 85 % hexane for elution. The title compound was obtained as a white power (606 mg) in 79 % yield. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.67 (2H, d, J = 8.09 Hz), 6.92 (2H, d, J = 8.07 Hz), 3.39 (2H, s), 2.15 (3H, s), 1.5-3.5 (10H, br). ^{13}C-NMR (75 MHz, $CDCl_3$) δ138.2, 134.9, 132.6, 94.3, 76.8, 74.8, 41.1, 24.1. HRMS (ESI) $[M-H]^-$: 373.1487, Calcd. for $C_{10}H_8B_{10}I$: 373.1462.

Compound 8: A 50 mL schlenk reaction tube was charged with H_2TPPBr_4, **7** (18.6 mg, 1 equivalent), $Pd(PPh_3)_4$ (4.6 mg, 0.2 equivalent), boronic acid **5** (58.4 mg, 10 equivalent), and anhydrous K_2CO_3 (55.2 mg, 20 equivalent). Anhydrous toluene (10 mL) was added via syringe. The mixture was degassed using the freeze-pump-thaw method three consecutive times. The reaction was then heated to 90 ℃ for three days. The resulting mixture was purified by silica gel flash chromatography using CH_2Cl_2 or $CHCl_3$ for elution. Two major fractions were collected; the first one is the compound **9** and second one is compound **8**. Dried the sample under vacuum, giving compound **8** 25 mg (78 % yield) and compound **9** 4.1 mg (15 % yield). Note: larger amount reaction (75 mg of compound **7**) gave similar yields. ^{1}H-NMR (250 MHz, CD_2Cl_2 with 0.1 % TFA) δ 8.30 (8H, br), 8.24 (4H, s), 7.67-7.70 (12H, m), 6.71-6.74 (16H, m), 3.20-3.22 (8H, m), 2.05 (12H, s), 1.5-3.5 (40H, br). MS (MALDI-TOF) M^+: 1600.24 Calcd. for $C_{84}H_{102}B_{40}N_4$: 1600.18. HRMS (ESI) $[M + H]^+$: 1601.2177, Calcd. for $C_{84}H_{103}B_{40}N_4$: 1601.2214. UV-vis (CH_2Cl_2 with 1% NEt_3) λ_{max} (nm): 433 (log ε 5.41), 527 (4.25), 600 (3.79), 670 (3.54). Compound **9:** ^{1}H-NMR (250 MHz, CD_2Cl_2) δ 8.69-8.72 (2H, m), 8.56-8.58 (2H, m), 8.47-8.49 (1H, m), 8.25-8.29 (2H, m), 7.68-7.80 (8H, m), 7.23-7.39 (12H, m), 6.96-6.99 (2H, d, J = 8.21), 6.87-6.91 (4H, m), 6.66-6.69 (4H, d, J = 7.03), 3.39 (2H,s), 3.17 (4H, s), 2.21 (3H, s), 2.14 (6H, s), 1.5-3.5 (30H, br), -2.38 (2H, br). MS (MALDI-TOF) M^+: 1353.62, Calcd. for $C_{74}H_{84}B_{30}N_4$: 1353.82. HRMS (ESI) $[M + H]^+$: 1354.9814, Calcd. for $C_{74}H_{85}B_{30}N_4$: 1354.9795. UV-vis

(CH_2Cl_2 with 1% NEt_3) λ_{max} (nm): 431 (log ε 5.51), 526 (4.41), 555 (sh, 4.18), 597 (4.05), 657 (3.72).

Compound 10: The method is similar to compound **8**. 1 equivalent $NiTPPBr_8$, 20 equivalent compound **3**, 0.4 equivalent $Pd(PPh_3)_4$ and 40 equivalent K_2CO_3 was refluxing in toluene for 7 days under Argon. Compound **10** was isolated by preparative TLC using 25 % DCM in hexane in 18 % yield. ^{1}H-NMR (250 MHz, CD_2Cl_2) δ 7.76 (8H, m), 7.24-7.32 (12H, m), 6.55-6.84 (32H, m), 3.18-3.34 (16H, m), 2.11-2.21 (24H, m), 1.5-3.5 (80H, br). MS (MALDI-TOF) $[M+H]^+$: 2643.807, Calcd. for $C_{124}H_{173}B_{80}N_4Ni$: 2643.174. UV-vis ($CH_2Cl_2$) λ_{max} (nm): 441 (log ε 5.11), 556 (4.04), 597 (3.93).

Compound 11: The method is similar to compound **8**. 1 equivalent of compound **12**, 3 equivalent of compound **3**, 0.1 equivalent of $Pd(PPh_3)_4$, 5 equivalent of K_2CO_3 was refluxing in toluene for 2 days under argon. Compound **11** was isolated by silica gel column using 30 % DCM in hexane in 87 % yield. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.91-8.94 (4H, m), 8.79 – 8.84 (4H, m), 8.18-8.22 (4H, d, J = 7.97 Hz), 8.08-8.09 (4H, m), 7.81 (2H, s), 7.54-7.57 (4H, J = 7.90 Hz), 3.78 (2H, s), 2.32 (2H, s), 1.53 (36H, s), 1.5-3.5 (20H, br), -2.73 (2H, s). MS (MALDI-TOF) $[M+H]^+$: 1180.91, Calcd. for $C_{68}H_{91}B_{20}N_4$: 1180.70.

Compound 14: H_2TPPF_{20} (19.5 mg, 20 μmol), compound **15** (35 mg, 200 μmol) and K_2CO_3 (28 mg, 200 μmol) were mixed into 5 mL DMF in a reaction tube. The mixture was stirred at room temperature for two days under ambient condition. Then KF (12 mg, 200 μmol) was added and the reaction mixture was refluxing for 2 hours. The mixture was poured into 50 mL KCl concentrated water solution and extracted with EtOAc (50 m L). The organic layer was washed three times by KCl solution. The solution was dried under vacuum and was purified by silica gel column using 50 % HPLC acetone in EtOAc. The major fraction was collected and recrystallized

in EtOAc and Hexane. The target purple powder was dried under vacuum, giving 20.4 mg in 61 % yield. ^{1}H-NMR (250 MHz, Acetone-d_6) δ 9.36 (8H, s), 2.40 (4H, s), 1.5-3.5 (36H, br), -2.35 (4H, br), -2.81 (2H, s). HRMS (ESI) M^{4-}: 388.9091, Calcd. for $C_{52}H_{53}B_{36}F_{16}N_4S_4$: 388.9071. Compound **16**: this compound was made using the similar method as compound **14**. Simply changed H_2TPPF_{20} to Chlorin **17** (20.6 mg, 20 μmol), Chlorin **17** was made according to the literature[48]. The target purple powder was dried under vacuum, giving 24.4 mg in 69 % yield. ^{1}H-NMR (250 MHz, Acetone-d_6) δ 8.89-8.92 (8H, m), 6.14 (2H, br), 4.03-4.06 (4H, m), 3.21-3.29 (2H, m), 2.75 (2H, s), 2.38 (2H, s), 1.5-3.5 (36H, br), -1.83 (2H, s), -2.51-2.56 (4H, br). HRMS (ESI) $[M+H]^{3-}$: 538.2360, Calcd. for $C_{55}H_{63}B_{36}F_{16}N_5S_4$: 538.2857

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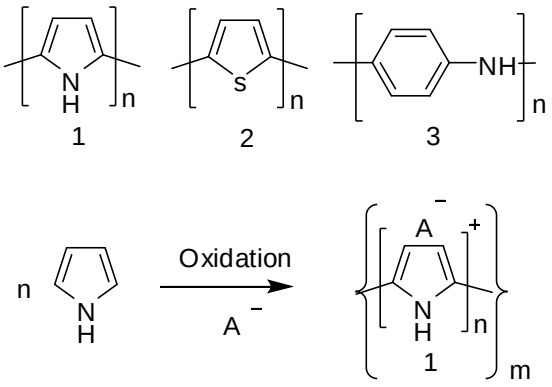
CHAPTER 4. SYNTHESES OF NOVEL CARBORANYL-FUNCTIONALIZED PYRROLES AND THIOPHENES FOR ELECTROPOLYMERIZATION

4.1. Introduction

Heterocyclic conjugated polymers[1] such as polypyrrole (**1**) and polythiophene (**2**) have found important applications as conducting electroactive materials, the electrochemical switching, energy storage and conversion, photovoltaics, electrochromic windows, electromechanical actuators, chemical sensors and physical sensors[2]. Since their discovery in the mid-1970s, conducting polymers have been a hot research area for many institutions as well as industrial lab. Ploypyrrole can be formed by the oxidation of pyrrole at a suitable anode. Upon application of a positive potential, an insoluble conducting polymeric material is deposited at the anode. Pyrrole can also be chemically polymerized by oxidant reagents, such as $FeCl_3$.



Scheme 4-1: Simplified polymerizations of pyrrole.

Polythiophenes have much in common with polypyrroles except that the synthesis of functionalized thiophenes is much easier to achieve than that of the pyrrole counterpart. Thiophene derivatives have different electropolymerization mechanism compared to that of pyrroles. While the electrochemical polymerization of pyrroles involves the radical anion intermediate, the electrochemical polymerization of thiophenes involves the radical cation intermediate. The generation of these radical cations during the electrochemical polymerization

process yielded the higher oxidation potential of many thiophene monomers than the resulting polythiophenes, a so-called "polythiophene paradox". Thus the electrochemical polymerization of thiophene to form polythiophenes remains a challenge in many cases[3]. This overoxidation phenomenon of polythiophenes results in deterioration in both chemical and physical properties of polymers. On the other hand, the electrochemical polymerization has many advantages, such as it can fast generate the functional polymers in one step onto a conducting surface and the polymer film thickness can be easily controlled from the consumed electric charge. Electronically conducting films could easily be electrodeposited on both macroelectrodes and ultramicroelectrodes with thicknesses ranging from nanometers to micrometers. Also, the electrochemical route allows the deposition of uniform films onto electrode surfaces of different shapes and geometries[4]. In order to maintain the advantages of the electrochemical polymerization process while achieving the polythiophenes with great conducting properties, the appropriate modification of the starting thiophene monomer becomes very necessary. Among those, the use of short thiophene oligomers, such as bithiophene and terthiophene, as starting material could minimize the overoxidation phenomenon during polymerization, but the conductivity of resulting polymers also was greatly sacrificed[5]. On the other hand, the presence of alkyl groups at the β-position of thiophene was also found to help reducing the "polythiophene paradox". Among those, the anchoring of an electron-withdrawing group to the thiophene β-position through a conjugated linker has a dramatic effect on the polymerization potential and the subsequent photovoltaic performance[6].

The electrochemical oxidation/reduction process of conductive polymers involves ionic movements with the surrounding ions of the electrolytic solutions. It is well-known that some counter- anions could lead to the side reactions such as overoxidation, the morphological

changes or conductivity changes of the polymers. The functionalization of conjugated organic polymers with organoborane groups is particularly attractive due to their electron-deficient nature. The resulting polymers may be endowed with unusual electronic properties[7]. Recently, the attachment of electron-deficient dimesitylboryl groups to the conjugated organic polymers was reported to significantly decrease the LUMO levels as evidenced by both a strong bathochromic shift in the UV-visible absorption and emission spectra and the observation of reversible reduction waves occurring at significantly less cathodic potentials[8]. Our group is interested in the preparation of conducting electroactive polypyrroles from carboranylpyrroles. Carboranes, members of the class boron clusters, are well known for their characteristic properties such as spherical geometry, remarkable thermal and chemical stability, and a very hydrophobic molecular surface. Moreover, it shows exceptional characteristics in both neutral and anionic forms. Carborane-containing organic molecules are very useful molecules and have wide applications in medicine[9-11] and materials areas[12-14]. The presence of carborane is believed to be able to greatly improve the thermal and/or chemical stability as well as the photo-and electrochemical properties of their host molecules. Several polymers containing carboranes have been synthesized and characterized[15-19]. In most cases, carboranes were linked to the host molecule by aromatic units (generally benzene). Those materials normally showed extreme resistance to combustion or remarkable thermal and oxidative stabilities. Carborane has strong electron-deficiency which could greatly reduce the energy for the π-π^* transitions. The presence of carborane group within an electronically conducting polymer film either as irreversibly immobilized doping anions or covalent binding had been proved to be able to reduce the communication between electrolyte anions and the polymer backbone due to its steric hindrance and high hydrophobicity. Teixidor's group and our group have synthesized polypyrrole films

functionalized with different carboranes.[20-23] Such type of redox-active polymers exhibited great improvement of their electrochemical stability and overoxidation resistance compared to unsubstituted polypyrroles. Lately, we envisioned to prepare conducting polymers from carboranylthiophenes besides the previously reported carboranylpyrroles. Thus the carborane moiety has been covalently attached to the β-position of thiophene through benzene spacer and it is expected that this would be helpful to reduce the oxidative voltage required for polymerization, and reduce the chance of the "polythiophene paradox" during the electrochemical polymerization process, without the large scarification of the conducting properties of polythiophenes.

It is known that the mechanical properties of polypyrroles and polythiophenes can greatly influence their functionality and these mechanical properties can vary widely. In order to design the suitable polymers with successful functional applications, it's very necessary to study the mechanic properties of polymers both at molecular and supramolecular levels. Many factors have been confirmed to be able to influence the mechanic properties of polymers. The composition of the monomers is one of them. It's believed that further study of polymers' mechanical properties needs to be performed at fundamental level at current condition. Among those, the most important study would be the development of the structure-property relationship, not only at supramolecular level but also at the molecular level. In our case, the strategy will start with the efficient synthesis of a library of carborane containing monopyrroles and monothiophenes. We interested in the synthesis of C-C linked carboranyl systems, which can give much more stable polymers. However, previously reported synthesis of 3-substituted carboranylpyrroles (**4**), the target molecules have been synthesized over six steps[17, 34-35]. Expensive carborane was introduced at the first step. As continued effort to develop metal-catalyzed reaction as reported in Chapter 3, we noticed that efficient and regioselective

brominations of pyrrole have been readily available[36], and the wide application of transition metal catalyzed coupling reaction in organic synthesis[37-38]. In this chapter[39], we designed a new regio-selective synthetic route for C-C bond linked carboranylpyrroles and carboranylthiophenes from these readily available pyrrole and thiophene derivatives based on the Suzuki-coupling reaction. We also described a general method for the synthesis of carborane derivatives and thiophenes through metal-catalyzed cross-coupling reactions using carborane substituted boronic acid or aromatic halogens. Thus, about twenty novel carboranyl pyrroles and thiophenes were synthesized. Also reported here is the electrochemical preparation of carborane-substituted conducting polymers electrogenerated from some of these novel monomers.

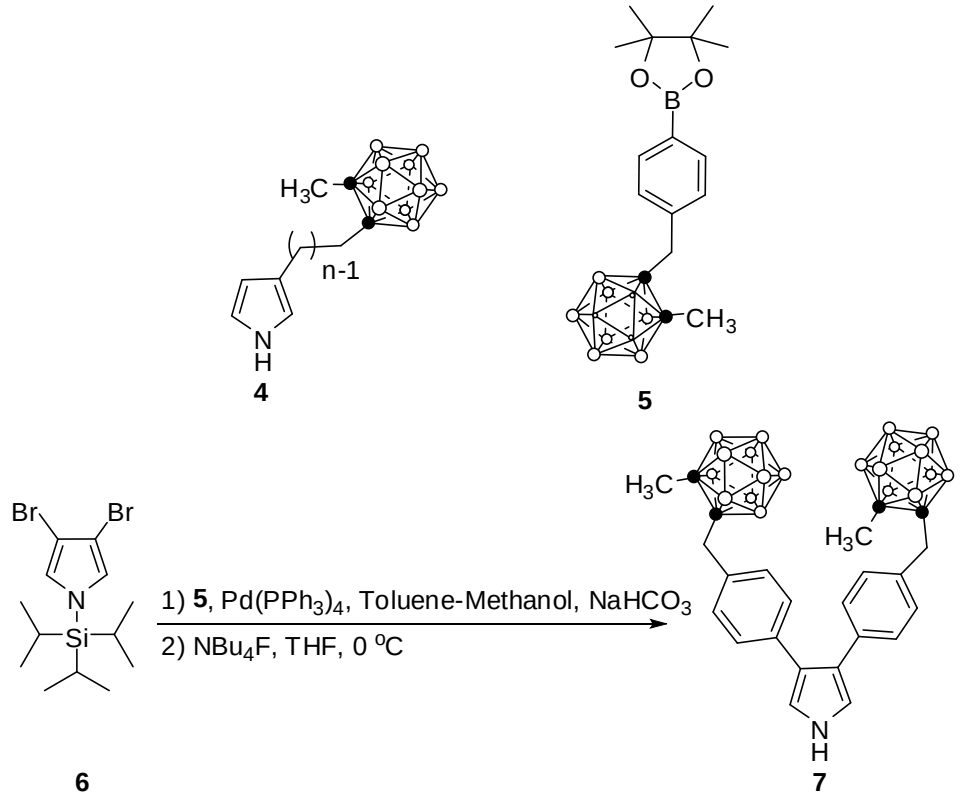
4.2. Synthesis of Pyrroles and Thiophenes Containing Carboranes at 3 / 4 Positions

Substitutions of pyrrole and thiophenes at 3 and 4 positions with bulky groups have several advantages: provide free volume and minimize cross-communication between adjacent polymer strands. Thus formed polymers can be called insulated polymers which can still maintain high conductivity. Our strategies for construction of the bulky carboranyl groups on pyrrole and thiophene are based on Suzuki coupling reaction. The target substitutions on the β-positions of the pyrrole/thiophene are also expected to enhance structural homogeneity as well as chemical stability by preventing interchain linkages and nucleophilic attack on polymer backbone. What is more, as we previously said, the carborane modified polymers are going to have very good thermal stabilities, as found in most carborane modified polymers.

4.2.1. Synthesis of Pyrrole Derivatives

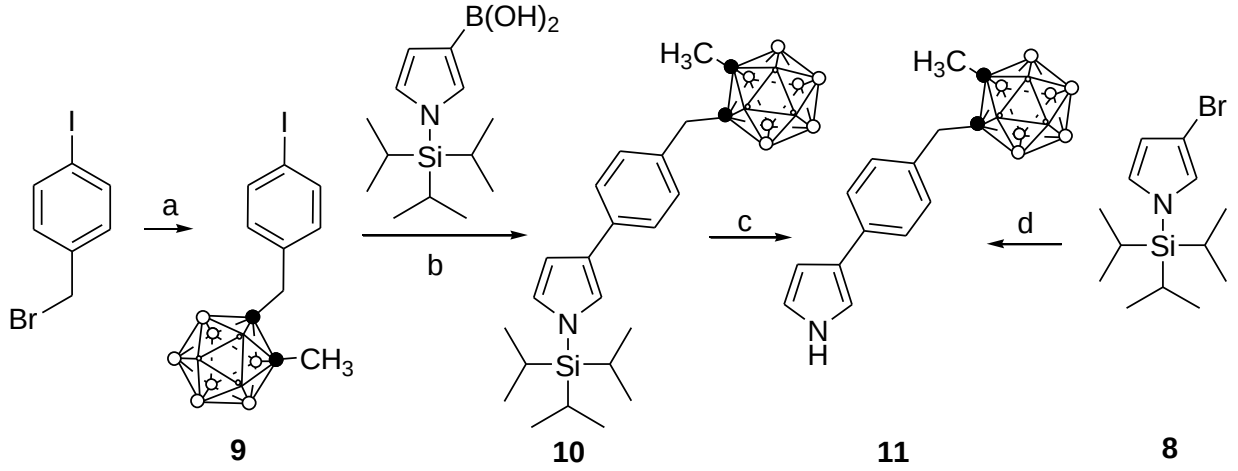
The carboranyl pyrroles syntheses started from compound **5**, which was synthesized in Chapter 3. Commercially available dibromopyrrole **6** reacted with carboranyl boronic ester **5** or

its boronic acid in the presence of $Pd(PPh_3)_4$ to produce di-carboranylpyrrole **7**, after deprotection using tetrabutyl ammonium fluoride (*Scheme 4-2*).



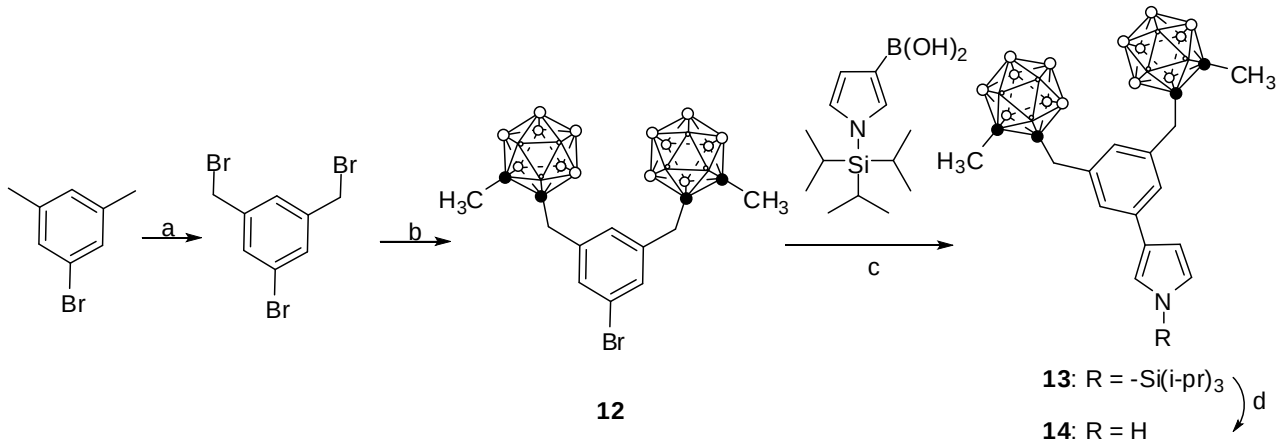
Scheme 4-2: Synthesis of the carborane 3,4-disubstituted pyrrole **7**.

The yield for the coupling reaction depended on the solvent and based used and the highest yield (32% overall) was obtained when $NaHCO_3$ and a 5:1 mixture of toluene and methanol were used. In anhydrous toluene using either K_2CO_3 or Na_2CO_3 as the base, the reaction was very slow and produced only ~ 3% of the target pyrrole **7**. The reason for this decrease in yield is the instability of the N-protected dibromopyrrole **6** under strong basic conditions. When mono-bromopyrrole **8** was used to substitute **7**, **11** was generated only in 17 % yield (*Scheme 4-3*), while the majority of **8** underwent polymerization. This difference might come from the reduced stability of mono-bromopyrrole **8** compared to that of di-bromopyrrole **6** under basic conditions.



Scheme 4-3: Carborane-substituted pyrrole (**11**) synthesis. Reaction conditions: a) 1-methyl-o-carborane, n-BuLi, THF; b) Pd $(PPh_3)_4$, Toluene/ Methanol, Na_2CO_3; c) NBu_4F, THF; d) Compound **5,** Pd $(PPh_3)_4$, Toluene/ Methanol, $NaHCO_3$, then NBu_4F, THF.

To improve the yield of **11**, an alternative approach was used. By coupling 1-(triisoprosilyl)pyrrole-3-boronic acid with carborane **9**, **11** was obtained in 89% yield. Started from the reaction of 1-methylbromide-iodobenzene with 1-methyl-o-carborane (activated by n-BuLi), compound **9** was isolated in 89% yield. The reaction of 1-(triisoprosilyl) pyrrole-3-boronic acid with **17** gave pyrrole **10** with similar yield (*Scheme 4-3*).



Scheme 4-4: Reaction conditions: a) NBS, CCl_4; b) 1-methyl-o-carborane, n-BuLi, THF; c) Pd $(PPh_3)_4$, Toluene/ Methanol, Na_2CO_3; d) nBu_4F, THF.

The structure of pyrrole **10** was confirmed by X-Ray (*Figure 4-1*). The Si–N distance is 1.779(2) A °, and the pyrrole ring is not quite coplanar with the phenyl ring, forming a dihedral angle of 6.1(7)u with it. Selective deprotection of 10 by using one equivalent of *n*-Bu_4NF in THF at 0 °C, yielded 11 in 95% yield. Controversy to the assumption that the presence of *n*-Bu_4NF might degrade the carborane cage into nido-carborane, any degeneration of the carborane cage was not observed under this reaction condition.

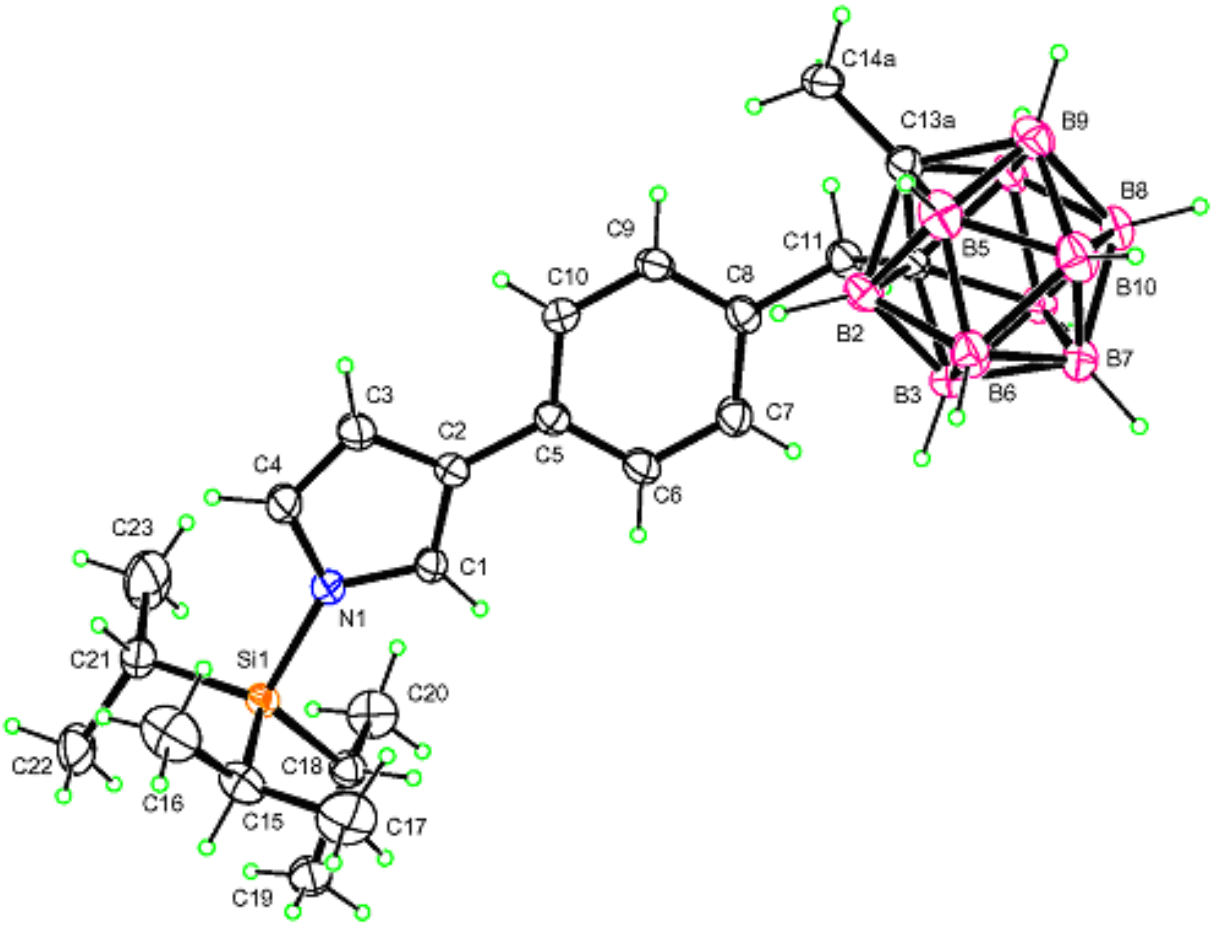
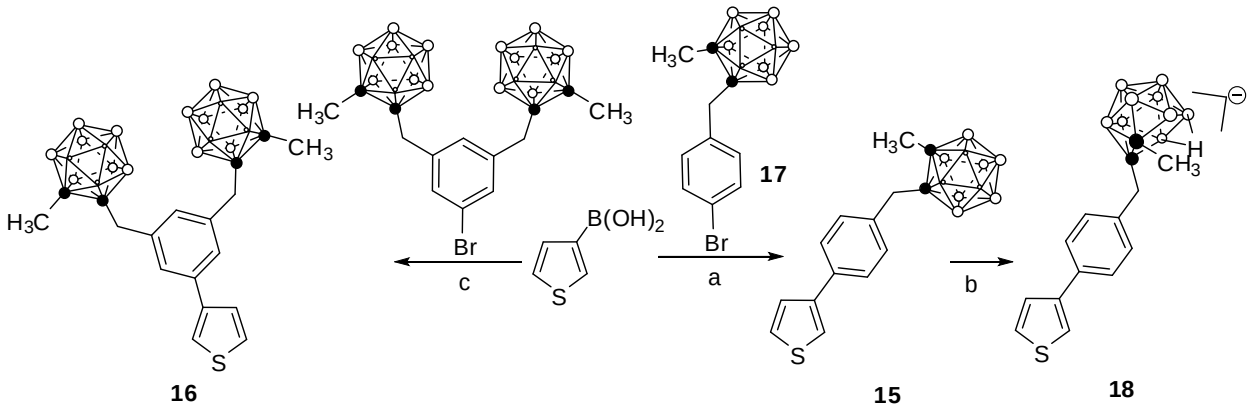


Figure 4-1: X-Ray structure of pyrrole **10**.

From this method, pyrrole **13** was also prepared starting from the organic halide **12**, which contained two carborane cages and was readily available using a previously reported two-step reaction[43] (*Scheme 4-4*). The selective deprotection of pyrrole **13** using a similar procedure gave **14** in 96% yield.

4.2.2. Synthesis of Thiophene Derivatives



Scheme 4-5: Synthesis of carborane-substituted thiophenes **15** and **16**. Reaction conditions: a) Pd $(PPh_3)_4$, Toluene/ Methanol, Na_2CO_3; b) *n*-Bu_4F, THF; c) Pd $(PPh_3)_4$, Toluene/ Methanol, Na_2CO_3.

To further test the versatility of this synthetic approach, it was explored to synthesize carboranylthiophenes. Compared to pyrrole derivatives, thiophenes are much more stable in most reaction conditions, which makes their syntheses much easier than that of pyrroles and usually no protection or deprotection steps are required. Started from thiophene-3-boronic acid, both carboranyl thiophenes **15** and **16** were synthesized with high yields, 94 % for **15** and 92 % for **16** respectively (*Scheme 4-5*). Among them, while the structure of **16** was characterized from mass and NMR, the structure of **15** has been confirmed by X-Ray diffraction as shown in *Figure 4-2*. The anionic *nido*-carboranylthiophene **18** was obtained in high yield by fluoride-induced deboronation of the *closo*-carborane cages using tetrabutylammonium fluoride. Carborane directly fused to thiophene was also synthesized, as shown in *Scheme 4-6*.

Compound **19** was synthesized straightforward from 3-ethylene thiophene and $B_{10}H_{14}$ in 50 % yield. Fluoride-induced deboronation of the *closo*-carborane cages using tetrabutylammonium fluoride gave **20** in 95 % yield. It was found compound **19** are easier to degrade than that of compound **15**.

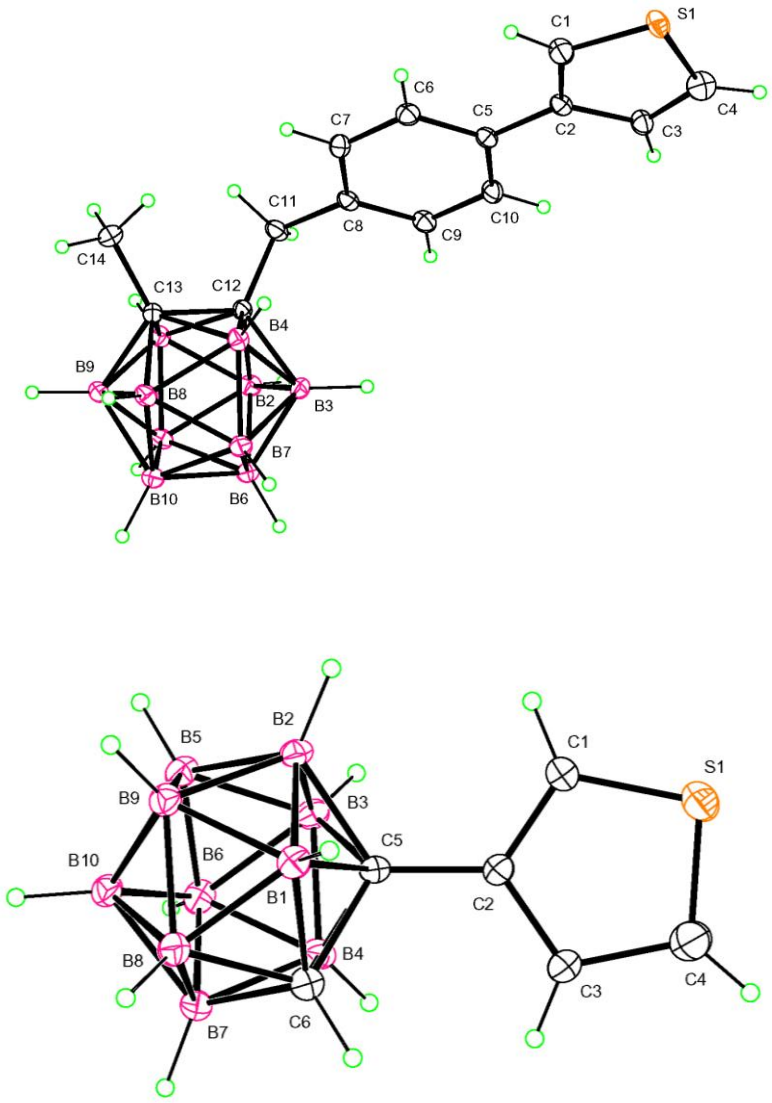
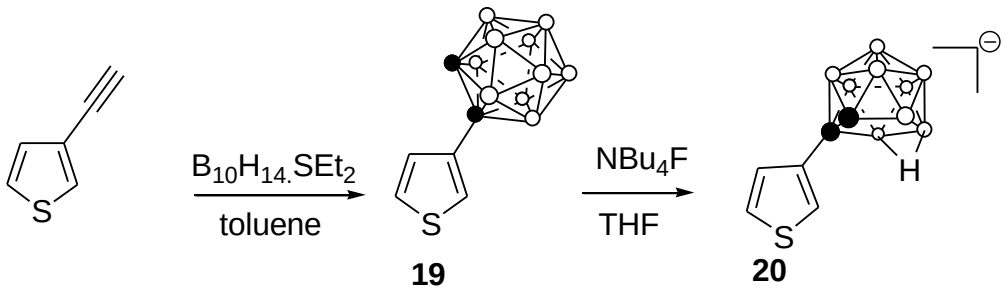
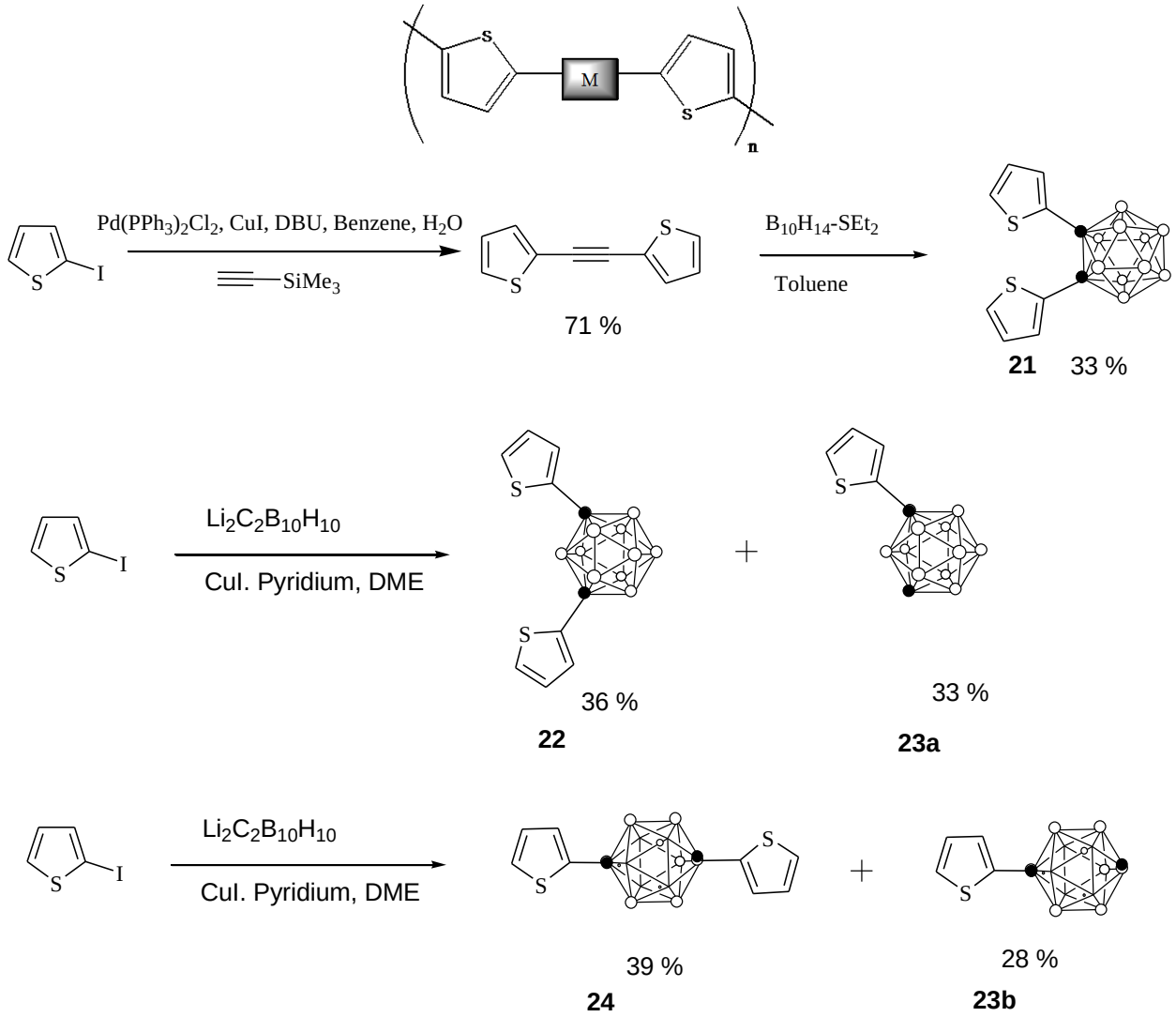


Figure 4-2: X-Ray structure thiophene **15** (left) and **19** (right).



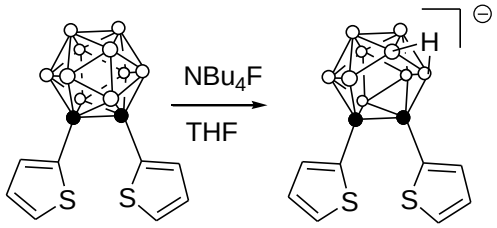
Scheme 4-6: Synthesis of carborane-substituted thiophenes **19** and **20.**

4.3. Synthesis of 2, 2'-Carboranyl Pyrroles and Thiophenes



Scheme 4-7: Synthesis of carborane-substituted thiophenes **21-24**.

Previous studies showed that introducing of carboranes into the polypyrrole improved the overoxidation threshold and thermal stabilities of the polymers. We are interested to embed the carborane cages into the backbone of polymer which was expected to provide novel electrochemical and mechanical properties of the resulting polymers. More importantly, as an interesting candidate for application in organic field effect transistors, polythiophenes-especially fully conjugated polymerthiophenes are found to have the poorer electrical performances in air



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Scheme 4-8: Synthesis of carborane-substituted thiophenes **25**.

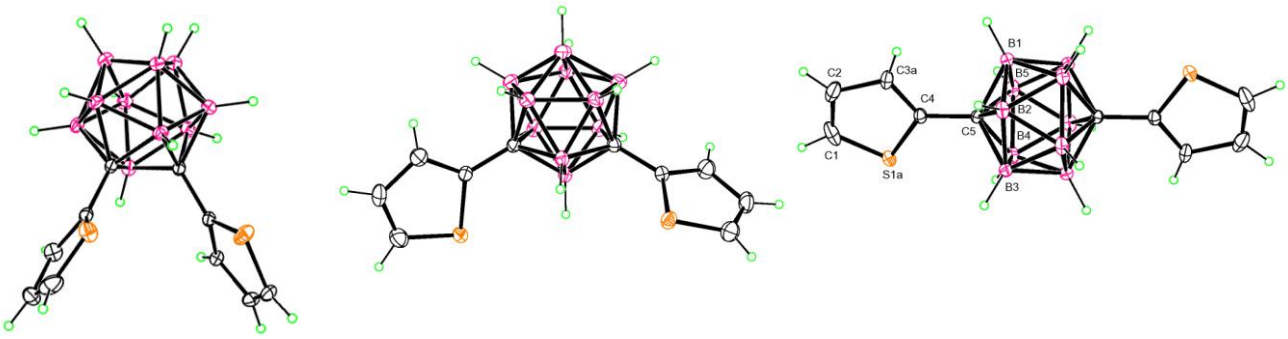


Figure 4-3: X-ray structures of **21, 22** and **24**. Only the major conformer of each disordered thiophene is shown.

than that under inert atmosphere. This is attributed to unintentional "p-type" doping of the semiconductor by interaction with oxygen. The stability of a polymer toward oxidative doping can be improved by increasing its ionization potential, which is somehow dependent on the effective π conjugation length of the polymer backbone. Control the effective π conjugation length of the polymer backbone can be achieved either by reducing π overlap between adjacent thiophene rings, or electronically by introducing a non or less conjugated unit into the backbone, thereby inhibiting delocalization. Twisting adjacent thiophene rings can be achieved by introducing the steric hendrance groups to the backbond or surface of polymers, like the compounds we synthesized in the above section. Preventing delocalization can also be achieved by introducing none or less conjugated co-monomers, like the general structure showing below. Meanwhile, para-carborane unit has attracted attention in relation to electron-transfer process. It has recently been suggested that σ-bonded carbon cage structures may be used as electron tunnel

barriers in molecualr electronic circuits, and it has been calculated the matrix element of p-carborane relevant to electron tunneling[50]. Carborane has three isomers according to the different relative positions between two carbon atoms, which will provide monomers with different angels once substituted with thiophenes. It would be interested, at least theoretically, the properties study of the corresponding polymers of their isomers. The resulted polythiophenes will have short effective π-conjugation lengths and greater propensity to be oxidative doped, as well as high thermal stability.

Dithiophenes **21, 22** and **24**, bearing respectively an *ortho*-, *meta*- and *para*-carborane group were synthesized from 2-iodothiophene as shown in *Scheme 4-7*. Compound **21** was obtained in two steps, via the reaction of 2,2'-ethylenethiophene (which was prepared in one step by modified Sogoyashi coupling from 2-iodo-thiophene) [45] with decaborane, in 24 % overall yield. On the other hand, compounds **22** and **24** were prepared in a single step in 36 and 39% yields, respectively, via the coupling reaction of 2-iodothiophene with the dilithium salt of either *m*- or *p*-carborane, in the presence of cuprous iodide. The structures of the three 2,2'-carboranyl-dithiophene isomers were characterized by NMR, MS and X-ray structures.

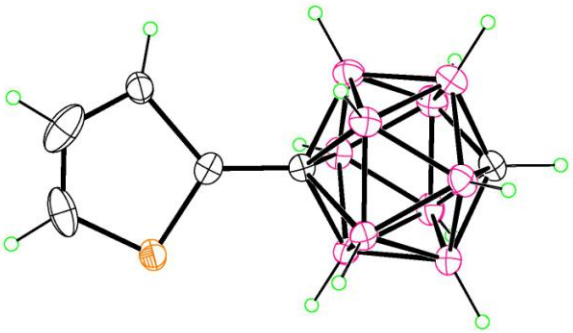
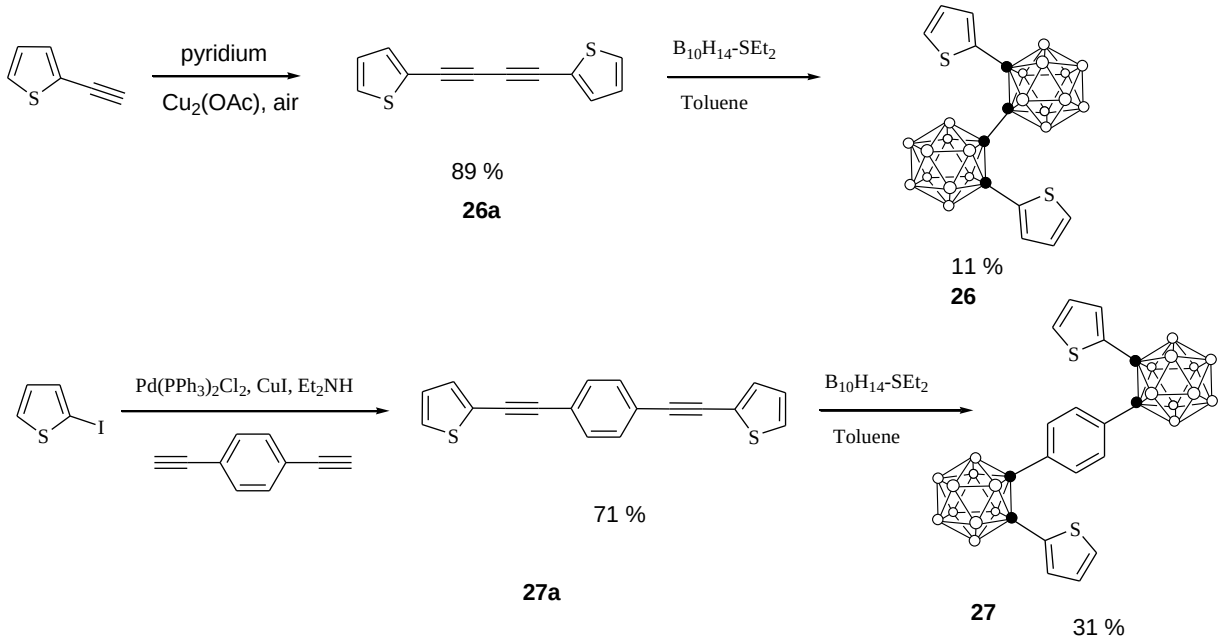


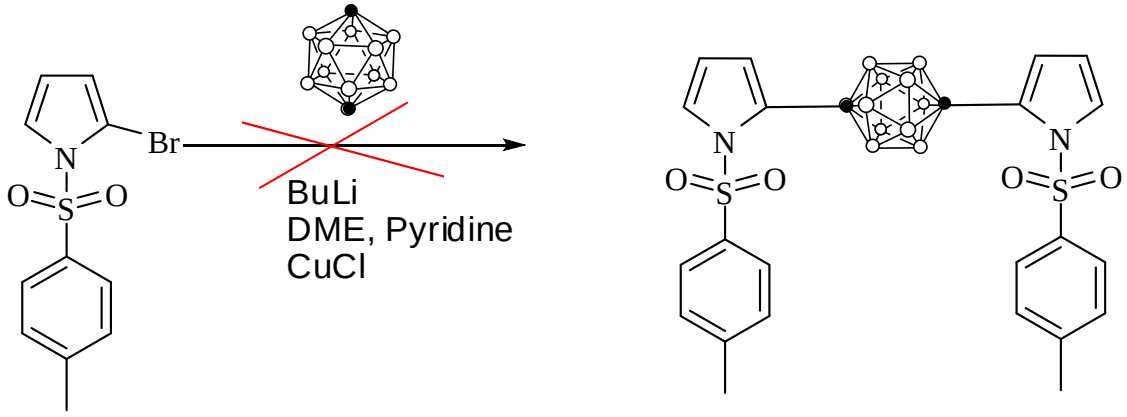
Figure 4-4: X-ray structures of **23b**.

In all three structures, thiophenes exhibit the common disorder by twofold rotation about the thiophene-carborane C-C bonds, swapping S and C positions. The *o*-isomer has two independent molecules, one having an ordered thiophene and a 56:44 disordered one, the other having an ordered thiophene and a 90:10 disordered one. The *m*-isomer has crystallographic C_2 symmetry, with the thiophene disordered 78:22. The *p*-isomer has crystallographic inversion symmetry, with thiophene disordered 75:25.

It was worthy to mention that the above reactions for **22** and **24** did give some side products and the major ones are the compounds **23a** and **23b,** as confirmed by NMR and in the case of **23b**, by X-ray structure (*Figure 4-4*). Obviously, they are the incomplete reaction products. They are separated by silica gel column with hexane and are less polar comparing to corresponding disubstituted compounds **22** and **24**. Further optimizing this reaction condition would possibly increase the yields, for example the using of excess amount of 2-iodothiophenes. Negative charged carborane containing monomers are very interesting because they can form self-doped polymers. Self-doped by bulky amphiphilic cages, such as the negative charged carborane are expected to increase the over-oxidation potential of resulting polymers. Among those, polypyrroles showed dramatically increased oxidation potential by introducing of cobaltocarborane anion as doping reagent. Inspired from my early work, which we degraded carborane into *nido* form to generate negative cage monomers, we also reacted compound **21** with NBu_4F to generate compound **25** in 95 % yield. Compound **25** is the first nido-carborane fused thiophenes that could potentially be used to provide negative charge delocalization in the backbone of the resulting polymer and once it is polymerized, this carborane-containing self-doped polymer would have interesting properties compared to the parent polymers.



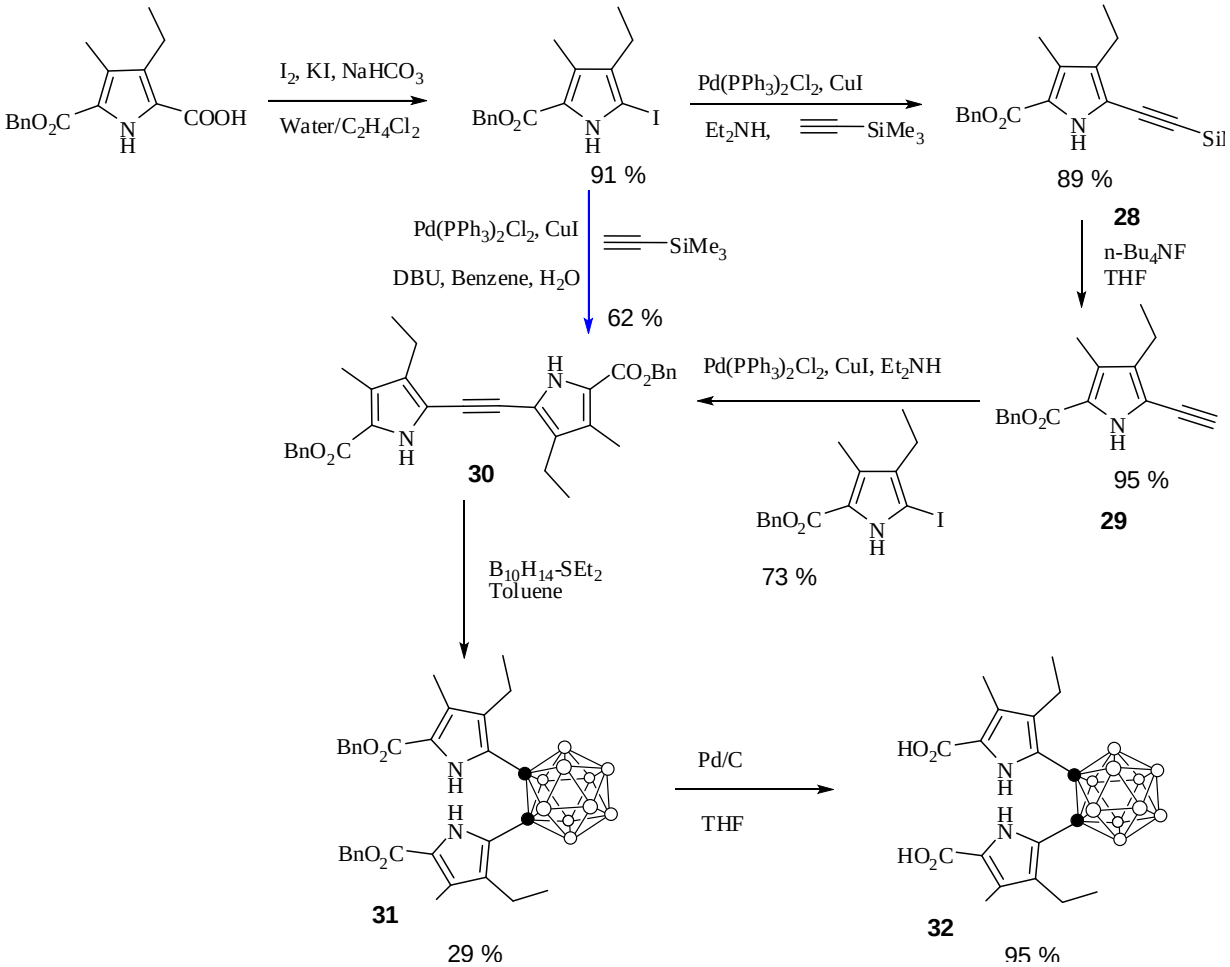
Scheme 4-9: Synthesis of carborane-substituted thiophenes **26** and **27**.



Scheme 4-10: Attempted synthesis of carborane-substituted bipyrrole.

Extending the above method, we synthesized compounds **26** and **27** in two steps. First, 2-ethylenethiophene was oxidized coupling to form compound **26a** in 89 % yield. Sonogashira coupling gave compound **27a** in 71 % yield. Carborane formation reactions were achieved in a similar method as described for compound **21**, from which compound **27** was achieved in 31 % yield, while compound **26** only isolated in 11 % yield. Also, compound **26** has very limited solubility in common organic solvent, thus the further electroproperty study of this compound was not performed. Compound **27** also found limited solubility, but I was still able to achieve the

decent NMR in chloform and the electropolymerization was able to perform in common organic solvent, such as DCM.



Scheme 4-11: Synthesis of carborane-substituted thiophenes **31-32**.

After successful embedding of carborane into thiophenes as described above, it was further used to modify pyrrole. Pyrrole derivatives are interesting because they can easily polymerize and also can be used to build porphyrin-liked macrocycles. However, directly coupling reaction in *Scheme 4-10* was failed. Only the debrominated product was isolated. It was attributed to the fact that bromo functional group is not active enough under this coupling condition. Most previous report used iodo group or activated bromo group for this type reaction. Further

reactions are expected to be successful by using readily available iodo-containing pyrroles and through protection of the pyrrole NH.

Attracted to the electropolymerization data of the o-carborane containing thiophenes synthesized, which gave the most conjugated and conductive polymers, We turned our attention to synthesize compound **31**, which o-carborane was embeded into the dipyrrole. The synthesis of **31** was shown in *Scheme 4-11*. The key intermediate **30** was ethylene bipyrrole. Although this type of compounds are very limited in the literature (only 4-5 examples according to SCI-finder), their syntheses are already developed[47, 48]. Started from 2-iodopyrrole, normally through three-step reactions, which including two Sonogashira coupling and a deprotection step. Although the methods are straightforward and similar to the literature it gave 60 % over yield from the three-step reactions, at least two column separations were required for the separation. Inspirited by recently developed one-pot synthesis of ethylene biaryls, a one-pot synthesis of the bipyrrole was developed by simple changing the base to DBU. The workup of the reaction was also very simple: after extracting by EtOAc, it only required methanol washing to achieve the pure product. The reaction gave 62 % yield without chromatography involved. The reactions are also very reproducible and constantly gave 55%-65% yields on 10 mol scale. Other solvent like CH_3CN gave similar results. In the future, I will test the effect of different substrates on this reaction.

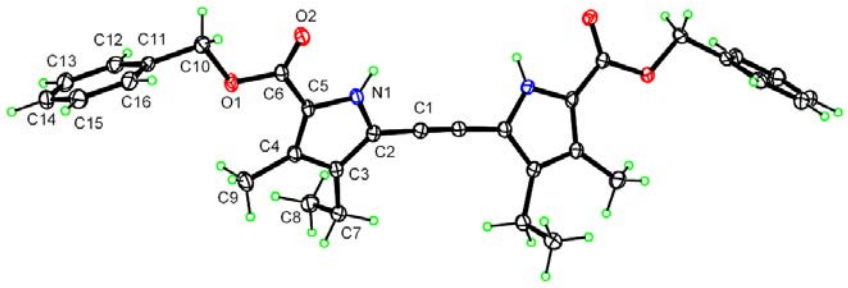


Figure 4-5: X-ray structures of **30.**

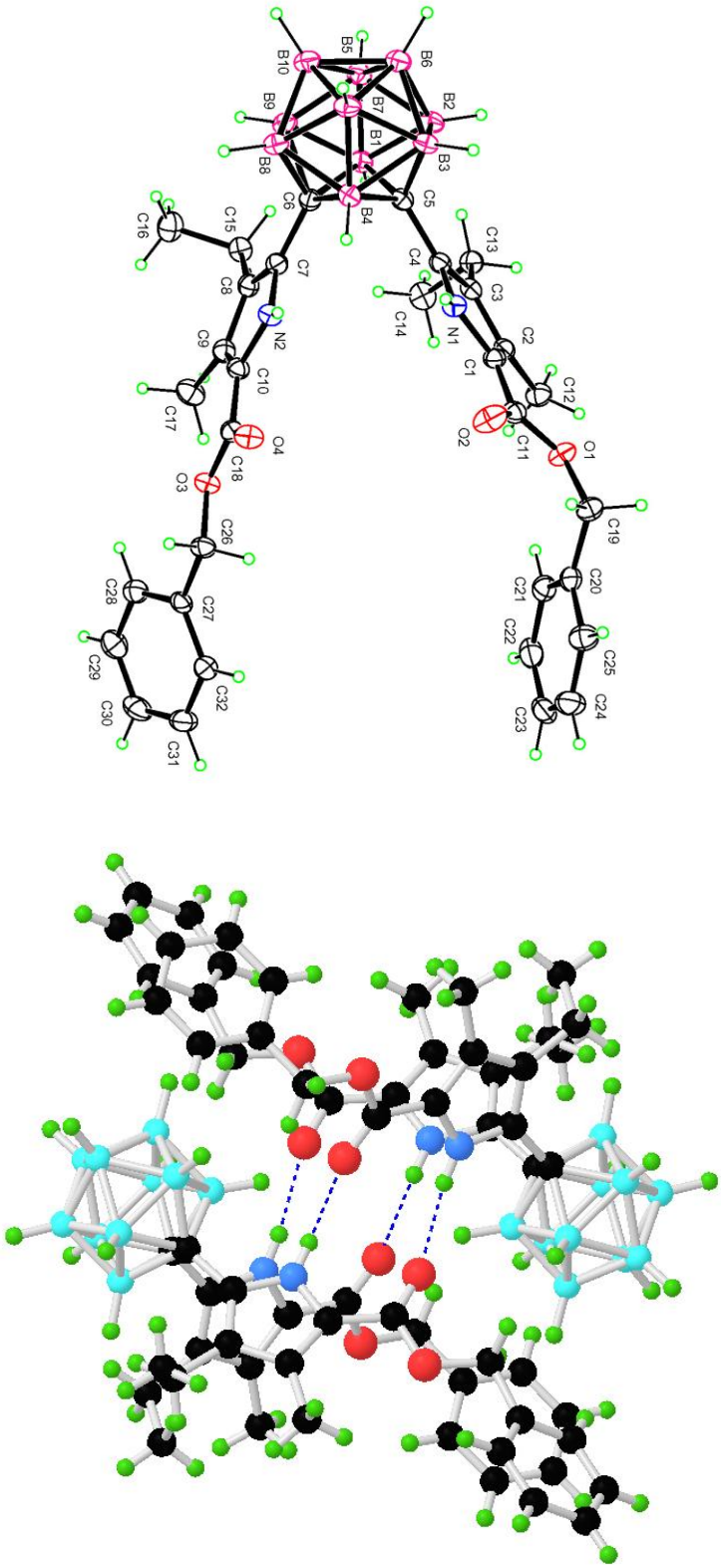


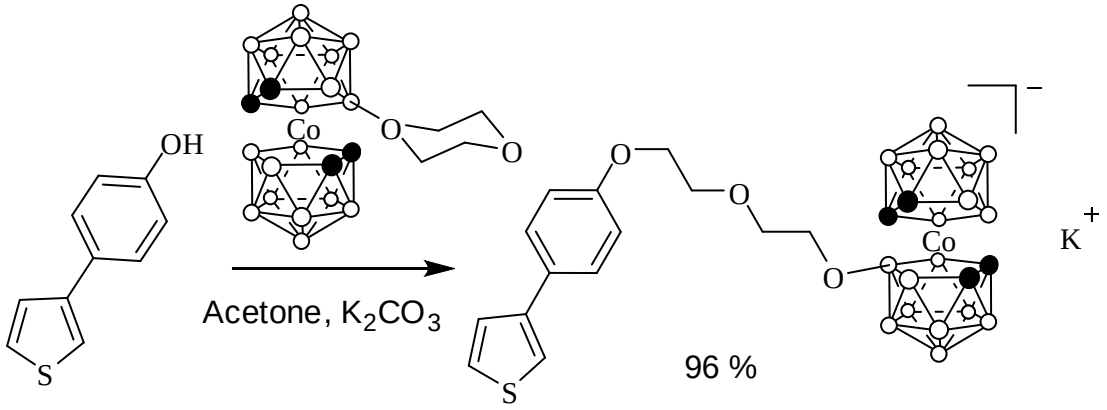
Figure 4-6: X-ray structures of **31** and its H-bonded dimer.

The X-ray structure of compound **30** was obtained by slow evaporation of the DCM solution of **30**. It showed that the two pyrroles are adjacent to each other. Compound **30** gave blue emission when excited at 360 nm. The interesting geometry and the blue emission of the bipyrrole make it interesting candidates for sensory anions. Compound **31** was achieved from reacting **30** with $B_{10}H_{14}$ and a reasonable 29 % yield was achieved. The crystal of **31** was obtained from diffusion of hexane into DCM solution of **31**. Its structure is shown in Figure 4-6. In solid state, the two pyrroles are cofacial to each other due to the insertion of carborane cage. More interesting, it formed a dimer due to the 4 hydrogen bonds between pyrrole NH and carbonyl groups. Further deprotection of **31** gave the free acid **32** in good yield. However, compound **32** is not very stable. Meanwhile, although several routs were tried for the decarboxylation, none of them is succeeded. Still, **32** is a very valuable starting material to built carborane containing macrocycles and also after iodination it can be used for metal-catalyzed polymerization reaction. Meanwhile, iodo groups can be removed to form 5, 5'-position free byprroles.

4.4. Synthesis of Metal-Containing Carboranyl Thiophenes

Carboranes are well known to form sandwich biscarbolide. They are analogs to the cyclopentadiene rings and can form sandwich structures with lots of metals, such as Fe, Co, Cu, Pd, Ni. Depending on the valence of the metal, the sandwich compounds can exist in a charged format with one or two negative charges or neutral format. We are interested in developing thiophenes containing metal biscarbolide, because it has many advantages over those thiophenes that containing the neutral carborane cages. First, it would generate metal containing polymers which have been a subject of extensive study because of transitional metal's ability to bind anions and small molecules or affect catalytic reactions. A central issue in the development of

conducting metal polymers is the proper control of the interactions between the metal centers and the conducting organic polymer backbone. Second, it would generate self-doping polymers due to the bulky negative biscarbolide (Cobaltocarborane here).



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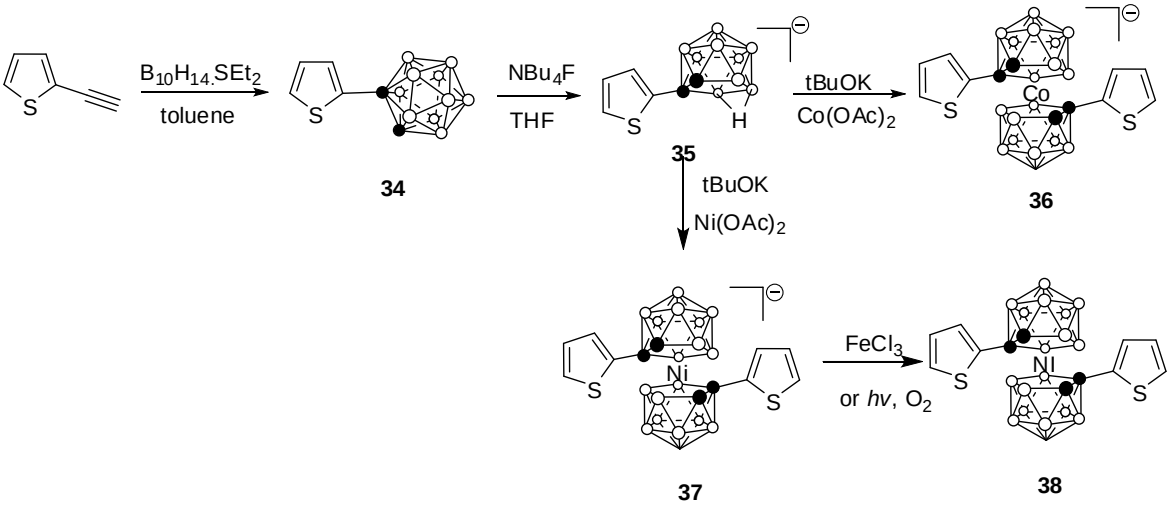
Scheme 4-12: Synthesis of carborane-substituted thiophenes **33**.



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Scheme 4-13: Synthesis of carborane-substituted thiophenes **36** and **38**.

As we mentioned before, cobaltocarborane anion was reported as a low coordinating anions for doping agents in organic conducting polymers. It showed dramatically improved overoxidation threshold. Third, It would generate conducting polymer actuator based on the rotation of biscarbolide. As reported by Dr. Howthorne, biscarbolide can rotate, which depends

the valence of the metal. The rotation can be controlled chemically (oxidation/reduction), electrochemically or photochemically.

As shown in *Scheme 4-12*, using the ring opening reaction in Chapter 2, we were able to isolate compound **33** in 96 % yield without column chromatography. Thus the efficient synthesis of compound **33** will also serve as a great advantage for its future application.

Next, we turned to synthesize compounds **36** and **38**. As we discussed above, these compounds contain metals in the backbone of the polymer and more importantly it could be find application as conducting polymer actuator. The synthesis is shown in *Scheme 4-13*. Compound **34** was synthesized in 71 % yield from $B_{10}H_{14}$. Then degradation using NBu_4F gave **35** in almost quantitatively as NBu_4 salt. Compound **36** was synthesized in one pot by mixing tBuOK and $Co(OAc)_2$ in DME. The reaction gave **36** after air oxidation 69 % yield. The method was better than NaH method, which needed two steps and normally gave lower yield. The compound **38** was synthesized in similar method but in a lower (15 %) yield. It was originally expected to be able to isolate compound **37**, because normally it need oxidation reagent to oxidize **37**(Ni^{3+}) to **38** (Ni^{4+}). However, in this reaction, although **37** can be detect by TLC, it quickly transformed into **38** by either oxygen or light. It is worth to notice that compound **38** could have different regioisomers according to literature. Both **36** and **38** gave a maximum UV-vis absorption peak at around 310 nm in acetone. Both of them are quite stable, giving molecular weight peak at HR-ESI, **36** even did not see the fragment peak (*Figure 4-14*) while **38** showed half-sandwich peak in 10 % intensity (*Figure 4-15*).

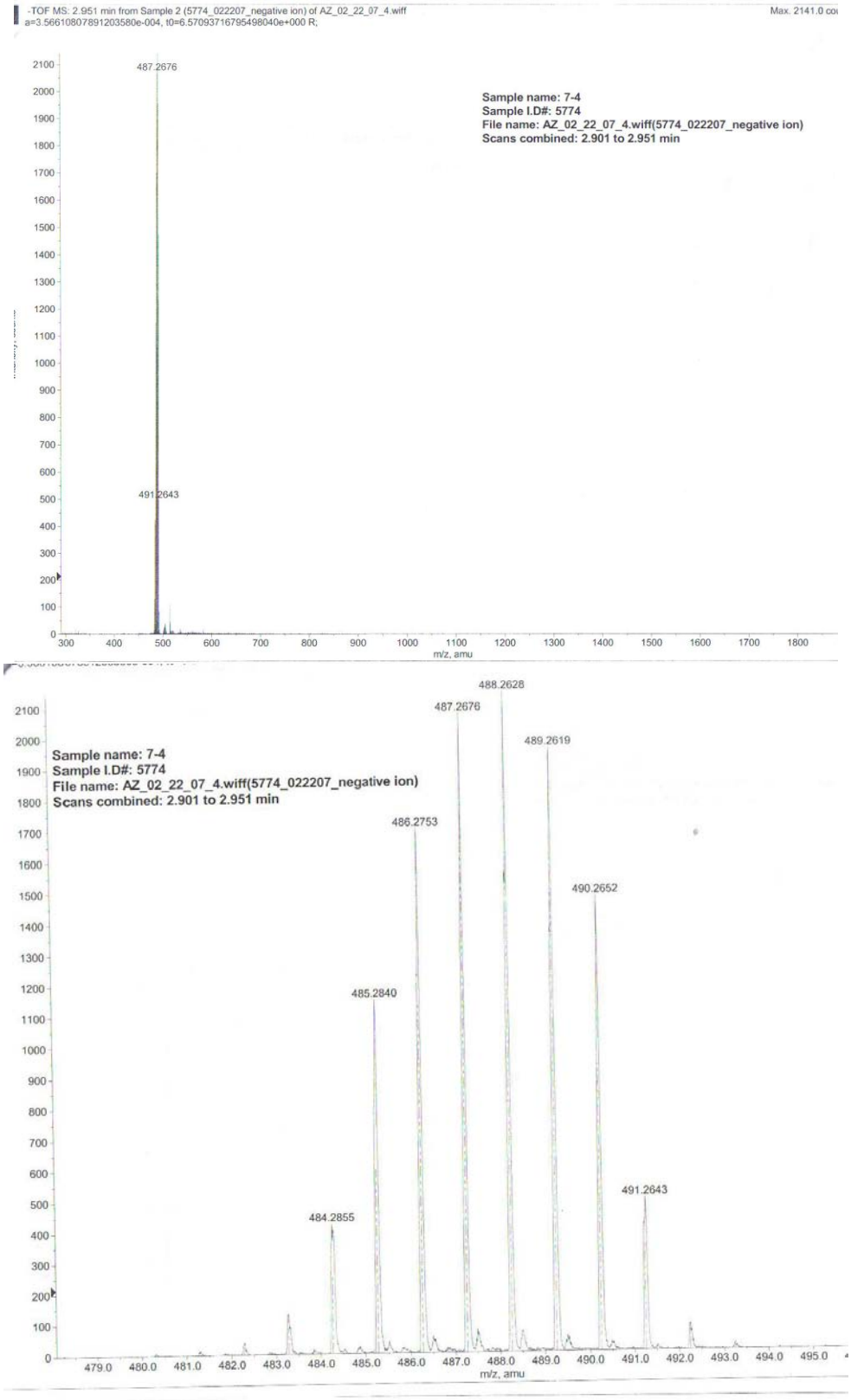

Figure 4-14: High resolution ESI MS of compound **36**. Bottom shows the isotope patterns (solid line) matched with the calculated ones (dot line).

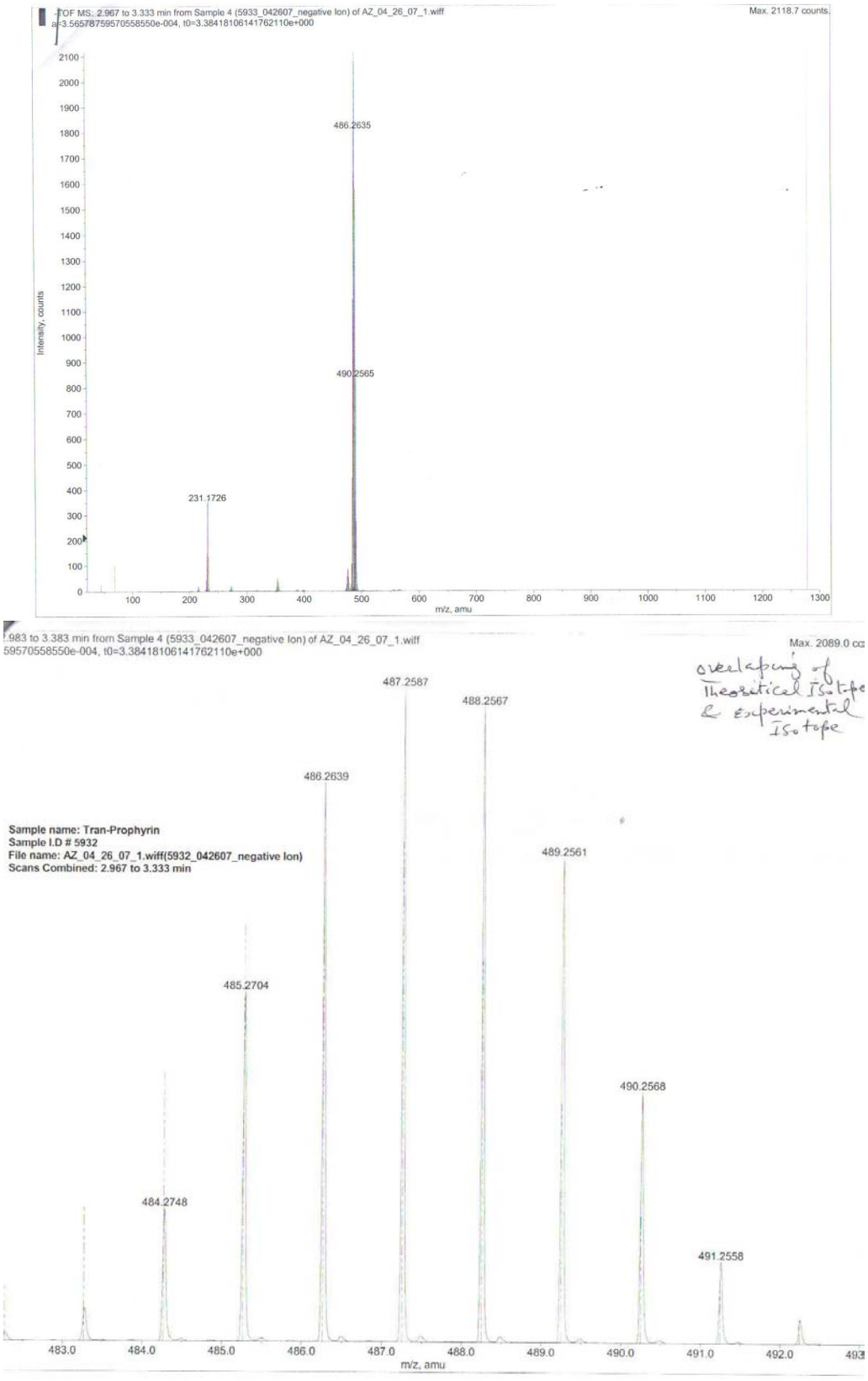

Figure 4-15: High resolution ESI MS of compound **38**. Bottom shows the isotope patterns (solid line) matched with the calculated ones (dot line).

4.5. Electrochemical Characterization of the Carborane-Substituted Monomers

The electrochemical characterization of the above compounds are collaborated with Dr. Bruno Fabro in France. Here we only show some summary data and further studies of the other compound mentioned above are still underway.

Table 4-1: Cyclic voltammetry data of different carborane-substituted pyrroles and thiophenes at 10^{-2}M in CH_3CN or CH_2Cl_2 + 10^{-1} or 2 x 10^{-1} M Bu_4NPF_6. Potential scan rate: 0.1 V s^{-1}.

Compound	E_{pa}^{mon} / V[a]	$E^{\circ\prime,poly}$ / V[b]
7	0.96 [c]	0.25 [c]
11	0.84 [c]	-0.01 [c]
14	0.92_5 [c]	[e]
	1.02 [d]	[f]
15	1.53 [d]	0.63 [d]
16	1.56 [d]	0.58 [d]
18	0.56, 0.85 and 1.74 [d]	[g]

[a] Irreversible anodic peak potential corresponding to the monomer oxidation. [b] Formal potential corresponding to the reversible *p*-doping/undoping of the electrogenerated conducting polymer (average of anodic and cathodic peak potentials). [c] In CH_3CN. [d] In CH_2Cl_2. [e] The compound did not electropolymerize whatever the tested experimental conditions. [f] Formation of soluble electroactive oligomers. [g] Passivation of the electrode surface occurred.

Among the carboranylpyrroles, the oxidation of **7** and **11** led to the formation of a conducting polymer deposit on the electrode surface. The cyclic voltammetry characterization of carborane-substituted pyrroles and thiophenes in CH_3CN or CH_2Cl_2 revealed an irreversible anodic peak in the range 0.84-0.96 V and 1.53-1.74 V corresponding to the oxidation of the pyrrole and thiophene rings, respectively (*Table 4-1*). For **18**, two further irreversible anodic peaks assigned to the oxidation of the anionic carboranyl cage were also observed at less positive potentials.

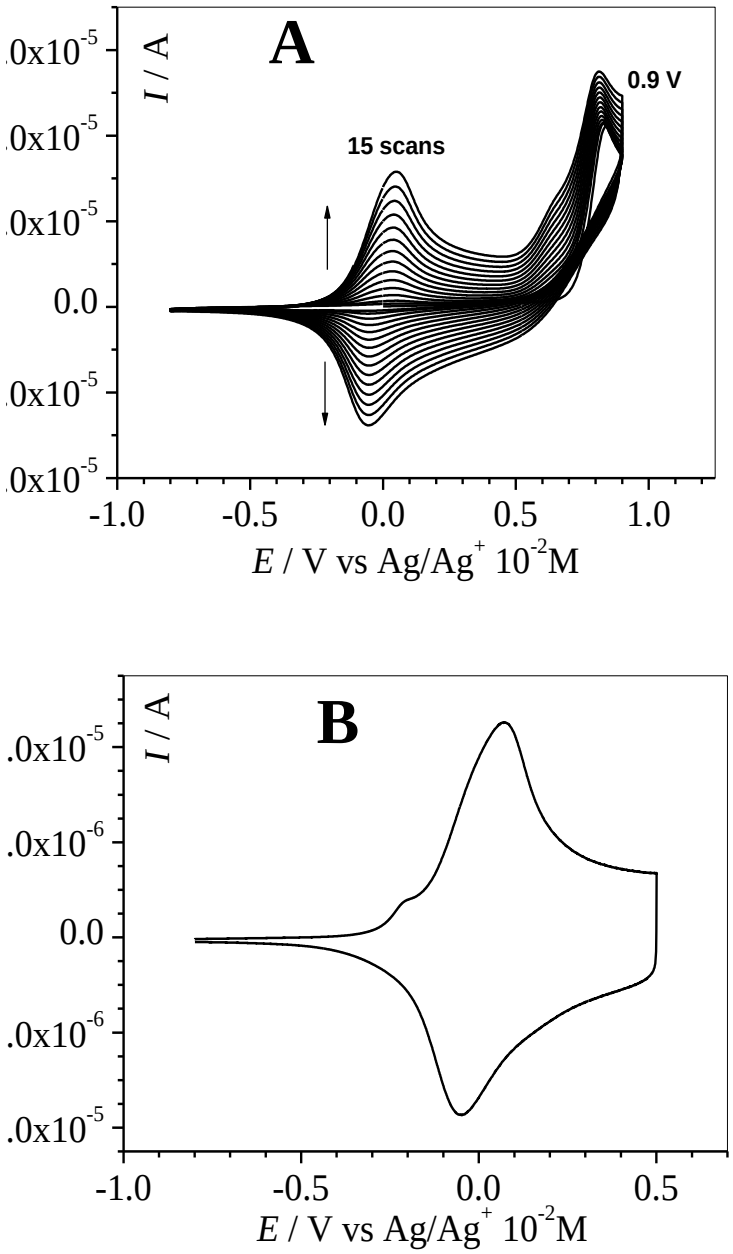

Figure 4-16: A) Successive cyclic voltammograms of 11 at 10^{-2} M in CH_3CN + 10^{-1} M Bu_4NPF_6 (0.1 Vs^{-1}); B) Electrochemical response of the electroformed polymer in CH_3CN + 10^{-1} M Bu_4NPF_6 at 0.1 V s^{-1} (electropolymerization charge: 64 mC cm^{-2}).

potentiodynamically or potentiostatically with no significant effect of the electropolymerization method on their respective electrochemical responses. As an example, typical cyclic voltammograms corresponding to the potentiodynamical electropolymerization of **11** are shown

in Figure 4-14A. The analysis of poly(11) in a monomer-free electrolytic solution showed a broad reversible redox system at ca. 0 V corresponding to the *p*-doping/undoping of the polypyrrole backbone (Fig. 4-14B). Compared with **11, 7** and its corresponding electrogenerated polymer were oxidized at more positive potentials as a result of the presence of two electron-withdrawing carboranes per pyrrole ring (Table 1). In contrast, **14** was found not to yield a conducting polymer deposit whatever the tested experimental conditions (namely, monomer concentration, oxidation potential and method, solvent).

4.6. Conclusions

In summary, we have successfully developed a new efficient synthetic route for a series of novel carboranylpyrroles and carboranylthiophenes. This synthetic route for preparing pyrrole and thiophene derivatives was based on metal-catalyzed cross coupling reaction, which was performed at mild reaction conditions and provided the target molecules with good yields.

4.7. Experimental

All reactions were monitored by TLC using 0.25 mm silica gel plates with or without UV indicator (60F-254). Carborane was detected by emerging into $PdCl_2$ in aqueous HCl solution (1 g $PdCl_2$ in 80 ml water and 20 ml concentrated HCl solution) and heated to see black spot on TLC. Silica gel Sorbent Technologies 32-63 μm was used for flash column chromatography. ^{1}H- and ^{13}C-NMR were obtained on either a DPX-250 or an ARX-300 Bruker spectrometer. Chemical shifts (δ) are given in ppm relative to $CDCl_3$ (7.26 ppm, ^{1}H), or CD_2Cl_2 (5.32 ppm, ^{1}H) unless otherwise indicated. Electronic absorption spectra were measured on a Perkin Elmer Lambda 35 UV-Vis spectrophotometer. MALDI-TOF mass spectra were obtained on an Applied Biosystems QSTAR XL, using positive method with dithranol as matrix unless otherwise

indicated. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Compounds **12**[43] and **17**[44] were prepared according to literature.

Compound 7: 1-(Triisopropylsilyl)-3, 4-dibromopyrrole **6** (460 mg, 1.24 mmol), **2** (1.15 g, 3.02 mmol) and tetrakis(triphenylphosphine)palladium (138 mg, 0.12 mmol) were added into a 250 mL Schlenk reaction tube. The solids were vacuumed and refilled with argon for three times. Then toluene (20 mL), methanol (4 mL) and 2 M $NaHCO_3$ solution (1.0 mL) were added through syringe at -78 °C. The reaction mixture was then "pump free throw" three times to remove air. Then the reaction mixture was stirred at 70 °C under argon for 2 days. The mixture was cooled to room temperature and poured into 100 mL brine and extracted by ethyl acetate (3 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in 20 mL THF. 1.25 mL nBu_4NF solution (1.0 M in THF) was added at 0 °C. The reaction mixture was stirred 0 °C for 20 min and then was poured into 100 mL water and extracted by ethyl acetate (3 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel, using 20 % ethyl acetate: 80 % hexane for elution. The title compound was obtained as a white power (222 m g) in 32 % yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, br), 7.18-7.21 (4H, M), 7.05-7.08 (4H, m), 6.94 (2H, d, J = 2.69 Hz), 3.45 (4H, s), 2.16 (s, 6H), 1.5-3.5 (20H, br). MALDI-TOF $[M+H]^+$: 560.74, Calcd. for $C_{24}H_{42}B_{20}N$: 560.82. HRMS (ESI) $[M-H]^-$: 558.5032, calcd. for $C_{24}H_{40}B_{200}N$: 558.5167.

Compound 10: 1-(Triisopropylsilyl)pyrrole-3-boronic acid (147 mg, 0.55 mmol), **9** (188 mg, 0.50 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) were added into a 50 mL Schlenk reaction tube. The solids were vacuumed and refilled with argon for three times. Then toluene (10 mL), methanol (2 mL) and 2 M Na_2CO_3 solution (0.5 mL) were added through syringe at -78 ℃. The reaction mixture was then "pump free throw" three times to remove air.

Then the reaction mixture was stirred at 80 °C under argon for 20 h until TLC indicated no compound **5** left. The mixture was cooled to room temperature and poured into 50 mL brine and extracted by ethyl acetate (3 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on aluminum (great III), using 15 % ethyl acetate: 85 % hexane for elution. The title compound was obtained as a white power (209 m g) in 89 % yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50 (2H, d, J = 8.19 Hz), 7.13 (2H, d, J = 8.31), 7.10 (1H, m), 6.82 (1H, m), 6.61 (1H, m), 3.45 (2H, s), 2.16 (3H, s), 1.5-3.5 (10H, br), 1.41 (3H, s), 1.11 (18H, m). MALDI-TOF $[M+H]^+$: 470.745, Calcd. for $C_{23}H_{44}B_{10}NSi$: 470.782. HRMS (ESI) $[M + Na]^+$: 492.4086, Calcd. for $C_{23}H_{43}B_{10}NSiNa$: 492.4078.

Compound 11: **10** (47 mg, 0.10 mmol) was dissolved in 5 mL THF. The solution was cooled to 0 °C for 15 min. 0.10 mL *n*Bu_4NF solution (1.0 M in THF) was added at 0 °C. The reaction mixture was stirred at 0 °C for 15 min until no starting material left and then was poured into 25 mL water and extracted by ethyl acetate (3 × 25 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was passed through a pad of silica gel, using 20 % ethyl acetate: 80 % hexane mixture for elution. The title compound was obtained as a white power (29.8 m g) in 95 % yield. ^{1}H-NMR (250 MHz, CD_2Cl_2) δ 8.43 (1H, br), 7.53 (2H, d, J = 8.19 Hz), 7.15 (2H, d, J = 8.31), 7.14 (1H, m), 6.84 (1H, m), 6.53 (1H, m), 3.48 (2H, s), 2.18 (3H, s), 1.5-3.5 (10H, br), ^{13}C-NMR (75 MHz, CD_2Cl_2) δ 136.1, 132.5, 131.0, 125.4, 124.4, 119.4, 115.2, 106.6, 78.8, 75.7, 41.2, 23.9. MALDI-TOF $[M+H]^+$: 314.367, Calcd. For $C_{14}H_{24}B_{10}N$: 314.442. HRMS (ESI) $[M-H]^-$: 312.2721, Calcd. for $C_{14}H_{22}B_{10}N$: 312.2721.

Compound 13: 1-(Triisopropylsilyl)pyrrole-3-boronic acid (547 mg, 2.05 mmol), **12** (996 mg, 2.00 mmol) and tetrakis(triphenylphosphine)palladium (116 mg, 0.10 mmol) were added into a 250 mL Schlenk reaction tube. The solids were vacuumed and refilled with argon for three times.

Then toluene (40 mL), methanol (8 mL) and 2 M Na_2CO_3 solution (4 mL) were added through syringe at -78 ℃. The reaction mixture was then "pump free throw" three times to remove air. Then the reaction mixture was stirred at 80 °C under argon for 20 h until TLC indicated no compound **12** left. The mixture was cooled to room temperature and poured into 150 mL brine and extracted by ethyl acetate (3 × 150 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel, using 15 % ethyl acetate: 85 % hexane for elution. The title compound was obtained as a white power (1.11 g) in 87 % yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, s), 7.03 (1H, m), 6.83 (1H, s), 6.78 (1H, m), 6.58 (1H, m), 3.47 (4H, s), 2.19 (6H, s), 1.5-3.5 (20H, br), 1.46 (3H, s), 1.13 (18H, m). MALDI-TOF $[M+H]^+$: 641.21, Calcd. for $C_{27}H_{58}B_{20}NSi$: 641.05.

Compound 14: 13 (640 mg, 1.00 mmol) was dissolved in 25 mL THF. The solution was cooled to 0 °C for 15 min. 1.1 mL *n*-Bu_4NF solution (1.0 M in THF) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min until no starting material left and then was poured into 25 mL water and extracted by ethyl acetate (3 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was passed through a pad of silica gel, using DCM for elution. The title compound was obtained as a white power (465 mg) in 96 % yield. ^{1}H-NMR (300 MHz, DMSO-d^6) δ 11.00 (1H, s), 7.37 (2H, s), 7.23 (1H, m), 6.90 (1H, s), 6.81 (1H, m), 6.43 (1H, m), 3.61 (4H, s), 2.25 (6H, s), 1.5-3.5 (20H, br). MALDI-TOF $[M+H]^+$: 484.57, Calcd. for $C_{18}H_{38}B_{20}N$: 484.72. HRMS (ESI) $[M-H]^-$: 482.4882, Calcd. for $C_{18}H_{36}B_{10}N$: 482.4854.

Compound 15: 3-Boronic acid thiophene (274 mg, 2.15 mmol), **17** (655 mg, 2.00 mmol) and tetrakis(triphenylphosphine)palladium (116 mg, 0.10 mmol) were added into a 250 mL Schlenk reaction tube. The solids were vacuumed and refilled with argon for three times. Then toluene (40 mL), methanol (8 mL) and 2 M Na_2CO_3 solution (4 mL) were added through syringe at -

78 °C. The reaction mixture was then "pump free throw" three times to remove air. Then the reaction mixture was stirred at 80 °C under argon for about 24 h until TLC indicated no compound **17** left. The mixture was cooled to room temperature and poured into 150 mL brine and extracted by ethyl acetate (3 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel, using 10 % ethyl acetate: 90 % hexane for elution. The title compound was obtained as a white power (620 mg) in 94 % yield. ^{1}H-NMR (300 MHz, CD_2Cl_2) δ 7.60 (2H, d, J = 7.69 Hz), 7.52-7.53 (1H, m), 7.43-7.44 (2H, m), 7.24 (2H, d, J = 7.91), 3.51 (2H, s), 2.19 (3H, s), 1.5-3.5 (10H, br), ^{13}C-NMR (75 MHz, CD_2Cl_2) δ 141.8, 135.8, 134.4, 131.2, 126.8, 126.8, 126.7, 125.5, 121.0, 78.3, 75.7, 41.1, 23.9. MALDI-TOF $[M+H]^+$: 331.65, Calcd. For $C_{14}H_{23}B_{10}S$: 331.50.

Compound 16: 3-Boronic acid thiophene (140 mg, 1.10 mmol), **12** (497 mg, 1.00 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) were added into a 250 mL Schlenk reaction tube. The solids were vacuumed and refilled with argon for three times. Then toluene (20 mL), methanol (4 mL) and 2 M Na_2CO_3 solution (2 mL) were added through syringe at -78 °C. The reaction mixture was then "pump free throw" three times to remove air. Then the reaction mixture was stirred at 80 °C under argon for about 24 h until TLC indicated no compound **12** left. The mixture was cooled to room temperature and poured into 100 mL brine and extracted by ethyl acetate (3 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel, using 10 % ethyl acetate: 90 % hexane for elution. The title compound was obtained as a white power (461 mg) in 92 % yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42-7.47 (1H, m), 7.35-7.37 (2H, m), 7.24 (2H, s), 6.92(1H, m), 3.50 (4H, s), 2.18 (6H, s), 1.5-3.5 (20H, br). MALDI-TOF $[M+H]^+$: 501.89, Calcd. for $C_{18}H_{37}B_{20}S$: 501.77.

Compound 18: Compound **15** (331 mg, 1.00 mmol) was dissolved in 50 mL THF. 2.1 mL *n*-Bu_4NF solution (1.0 M in THF) was added. The reaction mixture was stirred 60 °C for 2 h until no starting material left and then was poured into 50 mL water and extracted by ethyl acetate (3 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was passed through a pad of silica gel, using ethyl acetate for elution. The title compound was obtained as a white power (505 mg) in 90 % yield. ^{1}H-NMR (300 MHz, Acetone-d^6) δ 7.66-7.67 (1H, m), 7.57-7.60 (2H, m), 7.51-7.53 (2H, m), 7.36-7.39 (2H, m), 3.30-3.39 (8H, m), 3.27 (2H, s), 2.11 (3H, s), 1.76-1.81 (8H, m), 1.5-3.5 (9H, br), 1.40-1.44 (8H, m), 0.91-0.98 (t, 12H), -2.35 (1H, br s, B-H-B). MALDI-TOF $[M\text{-}NBu_4]^+$: 320.87, Calcd. for $C_{14}H_{22}B_9S$: 320.69.

Compound 19: Dodecarborane (1.22 g, 10 mmol) in 15 mL dry toluene was added diethylsulfane 2 g under N_2. The mixture was stirred at 40 ℃ for 3h and 60 ℃ for another 2h. Then 3-ethynylthiophene (1.08 g, 10 mmol) in 20 mL dry toluene was added and the reaction was refluxing for two days. Stopped the reaction and concentrated the reaction mixture. Added methanol 50 mL and stirred or sonicated for 30 min. The methanol solution was concentrated and dissolved into minimum amount of DCM. Silica gel column was used to separate the mixture, using 20 % DCM in hexane as mobile phase. The first major fraction was collected and dried under vacuum, giving white crystals 1.13 g in 50.3 % yield. ^{1}H-NMR ($CDCl_3$, 400MHz) 7.26-7.28 (1H, m), 7.21-7.23 (1H, m), 6.92-6.96 (1H, m), 3.75 (1H, s), 1.50-3.50 (br, 10H). MALDI-TOF M^+ 226.1. X-ray structure of title compound was grown by slow evaporation of DCM solution.

Compound 20: The method is similar to compound **18**. Compound **19** (338 mg, 1.50 mmol) was dissolved in 50 mL THF. 3.0 mL *n*-Bu_4NF solution (1.0 M in THF) was added. The reaction was finished in 30 min. The reaction gave target in 95 % yield. ^{1}H-NMR (Acetone-d_6, 250 MHz) δ

7.11-7.16 (1H, m), 7.01-6.08 (1H, m), 6.72-6.76 (1H, m), 3.39-3.41 (8H, m), 3.36 (1H, br), 1.77-1.79 (8H, m), 1.50-3.50 (br, 9H), 1.39-1.46 (8H, m), 0.95-1.02 (12H, m), -2.00-2.50 (1H, br). HRMS (ESI) $[M\text{-}NBu_4]^-$ Calcd. For $C_6H_{14}B_9S$ 214.1657, found 214.1668.

Synthesis of monomer 21: Synthesis of 2, 2'-ethylenethiophene was finished in 71 % yield according to literature[45].A mixture of decaborane($B_{10}H_{14}$) (0.36 g, 3.0 mmol) and Et_2S (1.80 mL, 7.5 mmol) in 15 mL of dry toluene was heated at 40 ℃ for 2 h under Argon, then raise to 60 ℃ for 3 h. Then 2, 2'-ethylenethiophene (0.38 g, 2.0 mmol) in 10 mL toluene was added into the mixture by syringe, the mixture was heated up at to 80 ℃ for two days under Ar. After TLC indicated no 2, 2'-ethylenethiophene left, cooled the reaction to room temperature and excess decarborane was destroyed by adding methanol. The solvent was removed under reduced pressure and ethanol was added to codistillation of Et_2S. The residue was purified by silica gel using 10 % dichlomethane in hexane, giving target compound 0.21 g in 33 % yield as white power. The crystals of **21** were grown by slow evaporation of its solution in dichloromethane. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.20-7.25 (4H, m), 6.82-6.85 (2H, m), 1.5-3.5 (10H, br). ^{13}C-NMR (63 MHz, $CDCl_3$) δ 134.9, 133.2, 129.9, 127.5, 81.4. MALDI-TOF $[M+H]^+$: 309.41, Calcd. for $C_{10}H_{16}B_{10}S_2$: 309.49.

Synthesis of monomer 22: The m-carborane (1.44 g, 10 mmol) in 30 mL dry 1, 2-dimethoxyethane was added dropwise a 1.60 M solution of *n*-BuLi in *n*-hexane (13.7 mL, 22 mmol) at 0 ℃ under Ar. The mixture was stirred for 30 min; then, dry CuI (4.2 g, 22 mmol) was added in one portion, and the mixture was stirred at room temperature for 2 h. Pyridine 6 mL, and 2-iodothiophene (4.6 g, 21 mmol) were added in one portion, and the resulting mixture was refluxed for two days. After cooling, insoluble materials were removed by filtration through Celite. The filtrate was washed with a 2 N HCl solution and water and brine, dried over $MgSO_4$,

and then concentrated. The residue was purified by silica gel column chromatography with hexane to give 1.10 g (36 %) of **22** (third fraction) as a colorless solid. The crystals of **22** were grown by slow evaporation of its solution in dichloromethane. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.14-7.16 (2H, m), 7.03-7.05-6.85 (2H, m), 6.84-6.88 (2H, m), 1.5-3.5 (10H, br). ^{13}C-NMR (63 MHz, $CDCl_3$) δ 138.6, 127.4, 126.9, 126.2, 72.8. MALDI-TOF $[M+H]^+$: 309.56, Calcd. for $C_{10}H_{16}B_{10}S_2$: 309.49.

Synthesis of monomer 24: Monomer **24** was prepared using the similar method as **22**. The compound was isolated in 39 % yield. The crystals of **24** were grown by slow evaporation of its solution in dichloromethane. ^{1}H-NMR (250 MHz, CD_2Cl_2) δ 7.09-7.11 (2H, m), 6.77-6.79 (4H, m), 1.5-3.5 (10H, br). ^{13}C-NMR (63 MHz, CD_2Cl_2) δ127.1, 127.0, 127.4, 125.4, 76.1. MALDI-TOF $[M+H]^+$: 309.39, Calcd. for $C_{10}H_{16}B_{10}S_2$: 308.49.

Compound 25: The method is similar to compound **18**. Compound **21** (310 mg, 1.0 mmol) was dissolved in 20 mL THF. 3.0 mL *n*-Bu_4NF solution (1.0 M in THF) was added. The reaction was finished in 30 min. The reaction gave target in 95 % yield as a white powder. ^{1}H-NMR (Acetone-d_6, 400MHz) 6.83-6.85 (2H, m), 6.52-6.57 (4H, m), 3.39-3.45 (8H, m), 1.75-1.87 (8H, m), 1.50-3.50 (9H, br), 1.38-1.50 (8H, m), 0.95-1.28 (12H, m), -2.00-2.50 (1H, br); ^{13}C-NMR (Acetone-d_6, 100 MHz) 147.5, 127.2, 125.4, 123.6, 76.0, 58.8, 23.9, 19.8, 13.4. HRMS (ESI) Calcd. $[M\text{-}NBu_4]^-$ $C_{10}H_{16}B_9S_2$, 297.1504, found 297.1562.

Compound 27: Compound **27a** was prepared in 71 % yield as a yellow powder using Sonogashira Coupling according to literature[46]. Synthesis of **27** is similar to the synthesis of monomer **21.** A mixture of dodecaborane (2.44 g, 3.0 mmol) and Et_2S (9.0 mL, 37 mmol) in 20 mL of dry toluene was heated at 40 ℃ for 2 h under Argon, then raise to 60 ℃ for 3 h. Then **27a** (1.45 g, 5 mmol) in 20 mL toluene was added into the mixture by syringe, the mixture was

heated up at to 80 ℃ for two days under Ar. After TLC indicated no **27a** left, cooled the reaction to room temperature and excess decarborane was destroyed by adding methanol. The solvent was removed under reduced pressure and ethanol was added to codistillation of Et_2S. The residue was purified by silica gel using 10 % dichlomethane in hexane, giving target compound 0.789 g in 31 % yield as light yellow power. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.33-7.34 (4H, m), 7.06-7.11 (2H, m), 6.97-6.99 (2H, m), 6.70-6.73 (2H, m), 1.5-3.5 (20H, br); MALDI-TOF $[M]^+$: 526.815, Calcd. for $C_{18}H_{30}B_{20}S_2$: 526.78.

Compound 28: To a solution of benzyl 4-ethyl-5-iodo-3-methyl-1H-pyrrole-2-carboxylate (3.69 g, 10 mmol) in diethylamine (100 mL) were added under argon (trimethylsilyl)acetylene (1.5 g, 15 mmol), dichlorobis(triphenylphosphine)palladium(II) (125 mg, 0.175 mmol), and copper(I) iodide (65 mg, 0.35 mmol). The homogeneous mixture was stirred at 50 °C for 2 h until TLC showed that no starting material left. After evaporation of the solvent in vacuum, the residue was subjected to chromatography on short silica gel column with *n*-hexane/dichloromethane/ethyl acetate (5:1:1) as eluent to give **28** (3.02 g, 89%).

Compound 29: To a solution of **28** (2.71 g, 8.0 mmol) in THF (50 mL) was added Bu_4NF (1.0M THF solution, 8 mL). After being stirred for 1 h, the resulting mixture was concentrated under reduced pressure. The crude residue was subjected to chromatography on a short silica gel column with dichloromethane as eluent to give white solid **13** (2.03 g, 95%) ^{1}H-NMR ($CDCl_3$, 250MHz) 9.19 (1H, s), 7.31-7.36 (5H, m), 5.28 (2H, s), 3.29 (1H, s), 2.47-2.50 (2H, m), 2.25 (3H, s), 1.00-1.11 (3H, m); ^{13}C-NMR ($CDCl_3$, 75 MHz) 161.2, 136.6, 133.7, 129.0, 128.9, 128.6, 126.5, 119.8, 114.1, 82.6, 75.5, 66.4, 18.4, 15.3, 10.8.

Compound **30**. Method A, To a solution of benzyl 4-ethyl-5-iodo-3-methyl-1H-pyrrole-2-carboxylate (1.85 g, 5 mmol) and **29** (1.34 mg, 5 mmol) in diethylamine (50 mL) were added dichlorobis(triphenylphosphine)palladium(II) (59 mg, 0.08 mmol) and copper(I) iodide (30 mg, 0.16 mmol). The homogeneous mixture was stirred at 50 °C for 3 h. After evaporation of the solvent in vacuum, the residue was subjected to chromatography on short silica gel column with *n*-hexane/dichloromethane/ethyl acetate (5:1:1) as eluent to give **30** (1.75 g, 73 %). Method B, A 250 mL Schlenk tube with Teflon-coated magnetic stir bar is charged with $PdCl_2(PPh_3)_2$ (210 mg, 6 mol%), CuI (188 mg, 10 mol%) and benzyl 4-ethyl-5-iodo-3-methyl-1H-pyrrole-2-carboxylate (3.69 g, 10 mmol). The system pumped with vacuum and refilled with nitrogen three times. Then dry benzene 40 mL, sparged with dry argon is added by syringe. Argon-sparged DBU (9.0 mL, 6 equiv) in 5 mL dry benzene is then added by syringe and ice-chilled thrimethylsilylethynylene (0.71 mL, 0.50 equiv) in 5 mL dry benzene is then added by syringe, followed immediately by distilled water (73 μL, 40 mol%). The reaction flask is covered in aluminum foil and left stirring at a high rate of speed for two days until no starting materials left on TLC, at the end of which the reaction mixture is partitioned in ethylacetate and brine (200 mL each). The organic layer is washed with 10% HCl (3 X 200 mL), saturated aqueous NaCl (1X 200mL), dried over $NaSO_4$, gravity-filtered and the solvent removed in vacuum. The crude product is washed with methanol and dried under vacuum, giving 1.57 g pure target. ^{1}H-NMR ($CDCl_3$, 250MHz) 8.86 (2H, s), 7.38-7.41 (10H, m), 5.31 (4H, s), 2.53-2.56 (4H, m), 2.30 (6H, s), 1.11-1.14 (6H, m); ^{13}C-NMR ($CDCl_3$, 75 MHz) 162.2, 137.7, 134.6, 133.6, 130.2, 129.8, 127.9, 121.2, 115.8, 86.6, 67.6, 19.8, 16.5, 11.9. MALDI-TOF M^+ 506.66.

Compound 31: Synthesis of **31** is similar to the synthesis of monomer **21.** A mixture of dodecaborane (2.44 g, 3.0 mmol) and Et_2S (9.0 mL, 37 mmol) in 20 mL of dry toluene was heated at 40 ℃ for 2 h under Argon, then raise to 60 ℃ for 3 h. Then **30** (1.06 g, 2 mmol) in 20 mL toluene was added into the mixture by syringe, the mixture was heated up at to 80 ℃ for two days under argon. After TLC indicated no **30** left, cooled the reaction to room temperature and excess decarborane was destroyed by adding methanol. The solvent was removed under reduced pressure and ethanol was added to codistillation of Et_2S. The residue was purified by silica gel using 25 % ethyl acetate in hexane, giving target compound 0.363 g in 29 % yield as light yellow power. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ^{1}H-NMR ($CDCl_3$, 300MHz) 8.60 (2H, s), 7.37-7.43 (10H, m), 5.27 (4H, s), 2.61-2.69 (4H, q), 2.18 (6H, s), 1.50-3.50 (br, 10H), 1.03-1.08 (6H, t); ^{13}C-NMR ($CDCl_3$, 75 MHz) 161.8, 137.2, 133.1, 130.2, 129.9, 129.8, 129.5, 122.1, 121.6, 84.6, 67.9, 18.9, 16.5, 11.8. MALDI-TOF M^+ 624.76.

Compound 33: 4-(thiophen-3-yl)phenol (170 mg, 1 mmol) and K_2CO_3 (160 mg, 1.1mmol) were mixed into 10 mL acetone and stirred for 30 min. Then [3, 3'-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)] (410 mg, 1mmol) was added and the reaction mixture was stirred overnight at room temperature. Filtered the solution to remove inorganic salt and the solution was partitioned by EtOAc and KCl water solution. Evaporated the solvent and dried under vacuum, giving the target in quantitative yield. Further precipitation from EtOAc and hexane gave the target organic powder 586 mg in 96 % yield. ^{1}H-NMR (300 MHz, Acetone-d_6) δ 7.40-7.56 (2H, m), 7.28-7.36 (2H, m), 7.21-7.24(1H, m), 6.91-6.95 (1H, m), 6.79-6.86 (1H, m) 4.17 (2H, br), 3.84 (4H, br), 3.67 (2H, br), 3.55 (2H, br), 3.43 (2H, br), 1.50-3.50 (18H, br).MALDI-TOF $[M+K]^+$ Calcd. for $C_{18}H_{36}B_{18}CoK_2O_3S$ 664.28, found 664.29.

Compound 34: The method is similar to compound **19**. Dodecarborane (2.44 g, 20 mmol) in 30 mL dry toluene was added diethylsulfane 4 g under N_2. The mixture was stirred at 40 ℃ for 3h and 60 ℃ for another 2h. Then 2-ethynylthiophene (2.16 g, 20 mmol) in 30 mL dry toluene was added and the reaction was refluxing for two days. The reaction gave 2.31 g title compound in 53 % yield. 1H-NMR ($CDCl_3$, 250 MHz) δ 7.25-7.27 (1H, m), 7.20-7.21 (1H, m), 6.90-6.92 (1H, m), 3.86 (1H, s), 1.50-3.50 (br, 10H). ^{13}C-NMR ($CDCl_3$, 63 MHz) 137.2, 130.4, 128.3, 127.7, 72.4, 63.7. MALDI-TOF M^+ 226.3.

Compound 35: The method is similar to compound **20**. Compound **34** (1.13 g, 5 mmol) in 50 mL THF. 10 mL *n*-Bu_4NF solution (1.0 M in THF) was added. The reaction was finished in 30 min. The reaction gave target in 94.3 % yield. ^{1}H-NMR (Acetone-d_6, 250 MHz) δ 6.95-6.96 (1H, m), 6.74-6.76 (1H, m), 6.65-6.67 (1H, m), 3.37-3.39 (8H, m), 3.35 (1H, br), 1.75-1.77 (8H, m), 1.50-3.50 (br, 9H), 1.37-1.45 (8H, m), 0.91-1.01 (12H, m), -2.03-2.50 (1H, br). HRMS (ESI) $[M\text{-}NBu_4]^-$ Calcd. For $C_6H_{14}B_9S$ 214.1657, found 214.1664.

Compound 36: Compound **35** (458 mg, 1 mmol) *t*BuOK (1.12 g, 10 mmol) and anhydrous $CoCl_2$ (1.3 g, 10 mmol) were mixed into 50 mL Schlenk reaction tube and 10 mL anhydrous DME was added by syringe. The reaction was refluxing for 30 h under nitrogen. Cooled to room temperature and filtered to remove inorganic salt. The filtrate was partitioned between DCM and nBu_4HSO_4 water solution. Dried under vacuum and passed through silica gel using DCM as elute. First major fraction was collected and dried under vacuum, giving yellow powder 251 mg in 69.7 % yield. ^{1}H-NMR (Acetone-d_6, 250 MHz) δ 7.22-7.24 (1H, m), 7.13-7.15 (1H, m), 6.89-6.91 (2H, m), 6.75-6.78 (1H, m), 6.63-6.64 (1H, m), 4.27 (1H, s), 3.41-3.47 (8H, m), 3.22 (1H, s), 1.76-1.78 (8H, m), 1.50-3.50 (br, 18H), 1.37-1.51 (8H, m), 0.95-1.01 (12H, m). HRMS (ESI) $[M\text{-}NBu_4]^-$ Calcd. For $C_{12}H_{26}B_{18}S_2Co$ 488.26, found 488.2628.

Compound 38: Compound **35** (458 mg, 1 mmol) *t*BuOK (1.12 g, 10 mmol) and anhydrous $NiBr_2$ (2.18 g, 10 mmol) were mixed into 50 mL Schlenk reaction tube and 15 mL anhydrous DME was added by syringe. The reaction was refluxing overnight under nitrogen. Cooled to room temperature and filtered to remove inorganic salt. The filtrate was partitioned between DCM and brine. Although the polar yellow spot could be detected in high percentage in the reaction mixture. However, during column on silica gel, major fraction was collected as a very nonpolar fraction, using 50 % DCM in hexane as elute, indentified as **38**, which dried under vacuum, giving yellow powder 37.1 mg in 15 % yield. ^{1}H-NMR (CD_2Cl_2, 250 MHz) δ 7.25-7.26 (2H, m), 7.02-7.03 (4H, m), 3.81 (1H, s), 3.22 (1H, s), 1.50-3.50 (br, 18H). HRMS (ESI) $[M-H]^-$ Calcd. For $C_{12}H_{25}B_{18}S_2Ni$ 487.2526, found 488.2567.

Electrochemical Characterizations.

Tetra-*n*-butylammonium hexafluorophosphate Bu_4NPF_6 was purchased from Fluka (puriss, electrochemical grade). Acetonitrile (Merck) was freshly distilled over calcium hydride prior to use. The electrolytic medium was dried *in situ* over activated, neutral alumina from Aldrich. Alumina was previously activated at 450 C under vacuum for several hours.

Linear potential sweep cyclic voltammetry experiments were performed with an Autolab PGSTAT 20 potentiostat from Eco Chemie B.V., equipped with General Purpose Electrochemical System GPES software (version 4.5 for Windows). The working electrode was a 1 mm-diameter platinum disk (area: 0.8 mm^2) and the counter electrode was a glassy carbon rod. Potentials were relative to the system 10^{-2} M Ag^+ | Ag in acetonitrile (+0.29 V vs aqueous SCE). Solution resistance was compensated by positive feedback. All electrochemical measurements were carried out at room temperature (20 ± 2 ℃) and under a constant flow of argon.

UV-visible Spectroelectrochemistry.

UV-visible absorption spectra were recorded on a Shimadzu Multispec-1501 spectrophotometer (190-1100 nm scan range) interfaced with a microcomputer for data acquisition and quartz SUPRASIL® cells from Hellma (1 cm pathlength) were used. The polymer films were grown on an indium tin oxide (ITO) coated glass slide electrode.

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CHAPTER 5. OXACALIXARENE-LOCKED PORPHYRINS AND CORROLES

5.1. Introduction

Multiporphyrin arrays[1] have attracted much interest because they play important roles in many areas such as in light harvesting[2], energy and electron transfer[3], and multielectron redox catalysis[4]. In these model systems, it is important to know how individual molecules within the array communicate with each other. Distance, orientation and geometry have been recognized as important factors for the control of this communication. Among covalently linked porphyrin arrays, cofacial porphyrins[5,6] have been widely studied in the past two decades. So far, the most successful cofacial porphyrins are the Pacman systems consisting of two etio-type porphyrins linked by a single rigid bridge (*Figure 5-1*). However, the synthesis of cofacial porphyrins and cyclic porphyrin arrays[7,8] has always been a challenge.

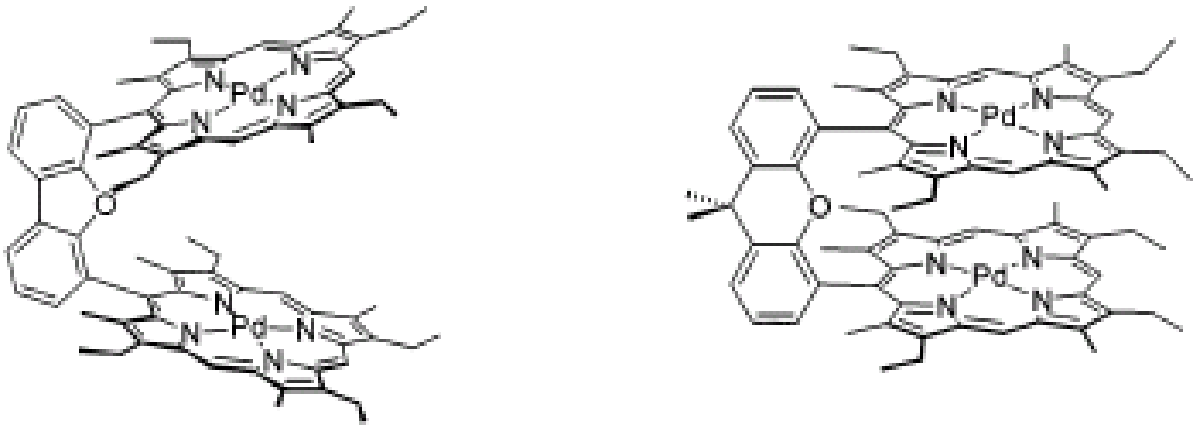


Figure 5-1: Common Pacman and "Hangman" porphyrin structures. From left to right, dibenzofuran linked Pacman porphyrin, xanthene linked Pacman porphyrin.

Calixarenes have been intensively studied in the past decade because of their unique conformational and cavity structures, and molecular recognition properties[9]. Recently, heteroatom-bridged calixarenes have received much interest because they are far less studied and they have novel chemical and physical properties[10]. Among them, oxygen-bridged

calix[4]arenes[11] belong to one of the first members of the calixarene family and recently the reaction was optimized by Katz, et al.[11b]. But surprisingly these types of compounds exist in very limited numbers, and no bigger macrocycles, such as oxacalix[6]arene and oxocalix[8]arene, have been reported in the literature. Unlike carbon linked calixarenes, which adopt different conformations such as cone, 1,3-alternating and 1,2-alternating conformations, oxacalix[4]arene normally adopts a 1,3-alternating conformation as proved by NMR spectroscopy and X-ray structures (all the X-ray structures reported to date show 1,3-alternating conformations).

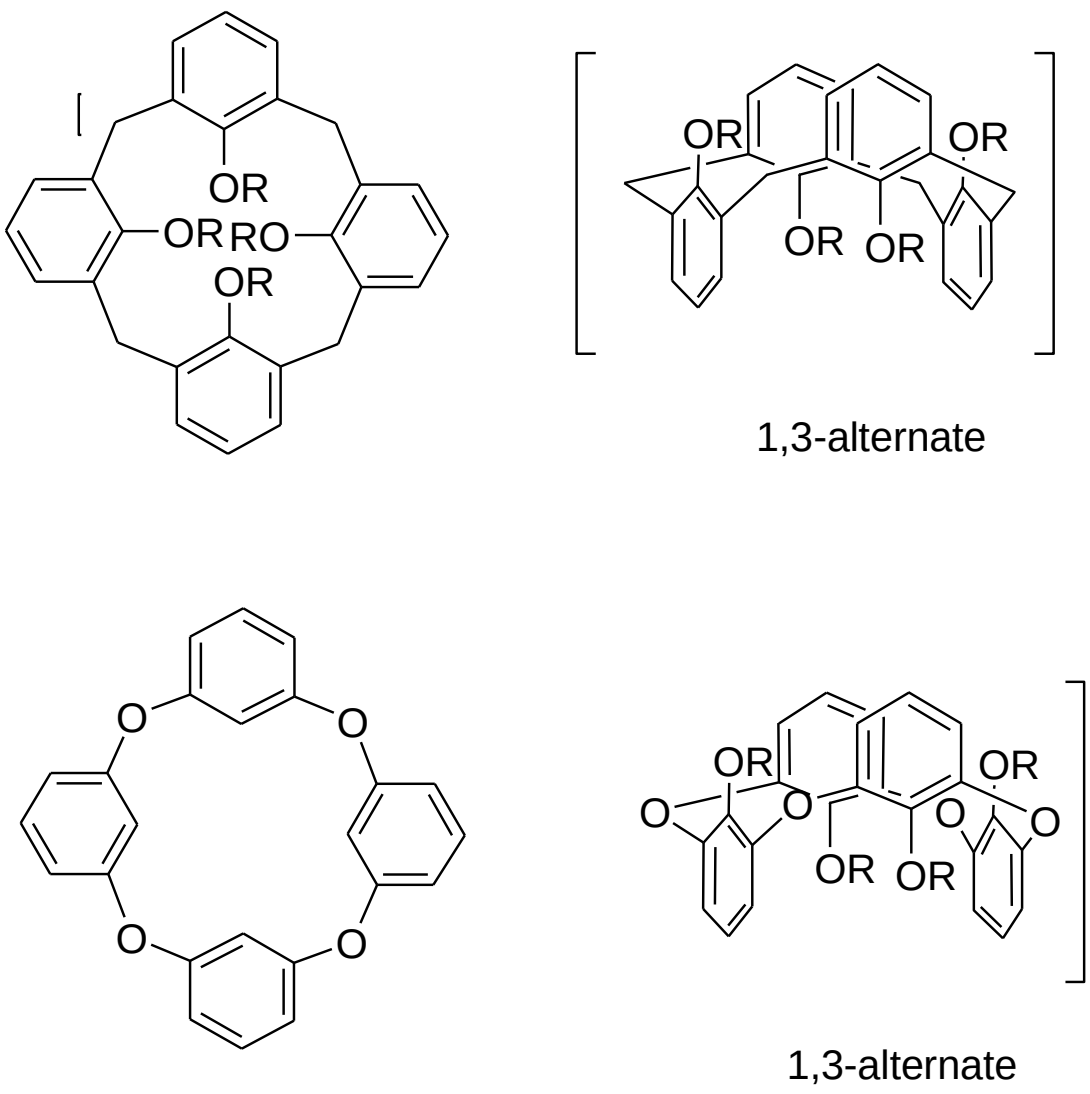
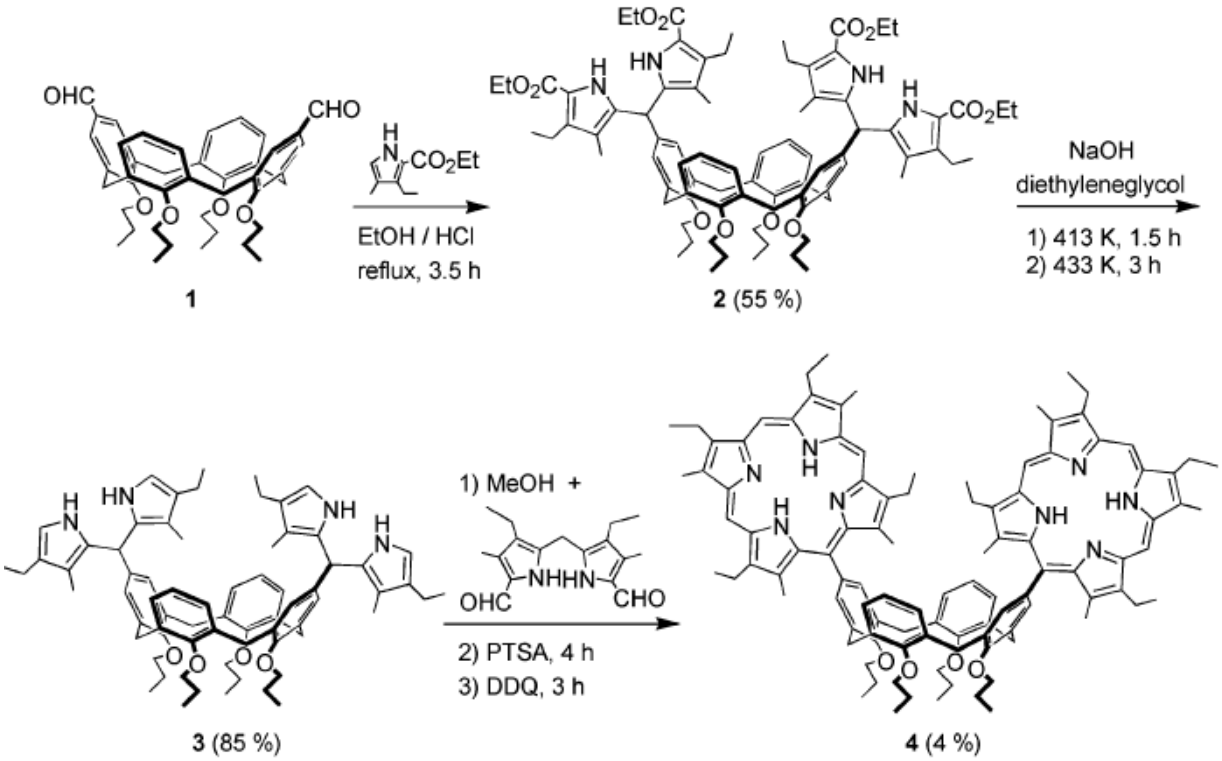


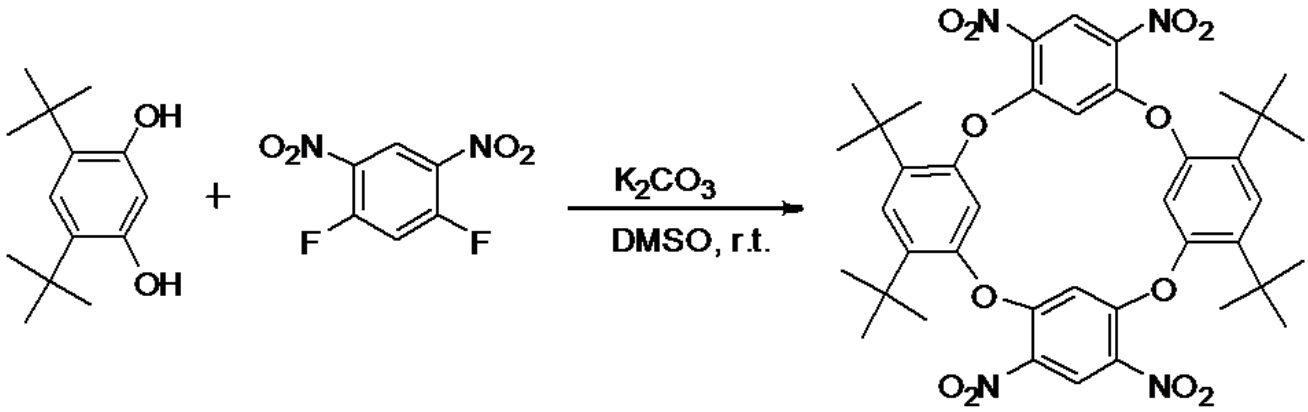
Figure 5-2: Calix[4]arene and oxacalix[4]arene chemical structure and 1,3-alternating conformations they adopt.

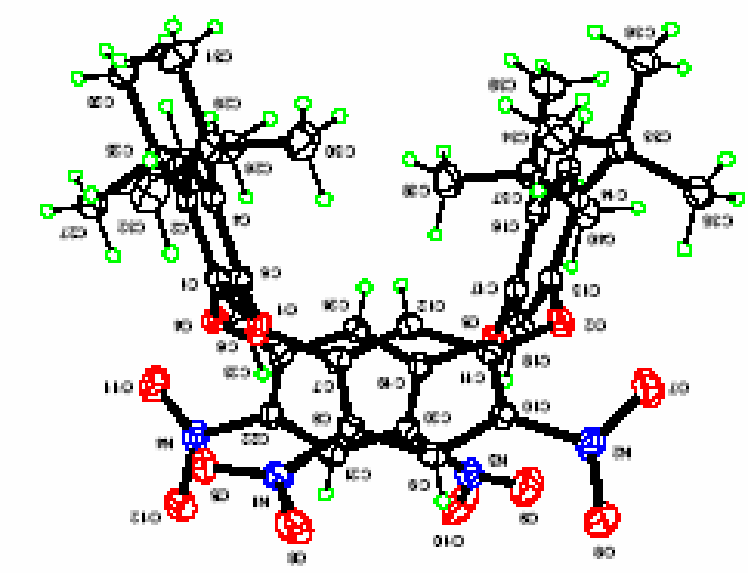


Scheme 5-1: Example of porphyrin-calixarene conjugates reported by the Harvey group[13a].

Due to the interesting properties induced by calixarenes and porphyrin, respectively, porphyrin-calixarene conjugates have been synthesized by several groups[12-14]. Most of them were synthesized by modification of calixarenes. Despite of the long synthetic routes, the conformations of the resulting conjugates are often very flexible[13]. As shown in *Scheme 5-1*, the total synthesis of porphyrin-calixarene conjugates gave very low yields. We envisioned that oxacalix[4]arenes usually adopt very clean 1,3-alternaing conformations which provide us with the possibility to design and synthesize oxacalixarene-locked cofacial bisporphyrins. In this Chapter, we describe the efficient selective synthesis, X-ray crystallography, and physical properties of a novel oxacalix[4]arene-locked cofacial porphyrin dimer. Also, by slightly changing the reaction conditions, we report the first formation of oxacalix[6]arenes and oxacalix[8]arenes.

5.2. Synthesis and Characterization of Calixarene Linked Porphyrins



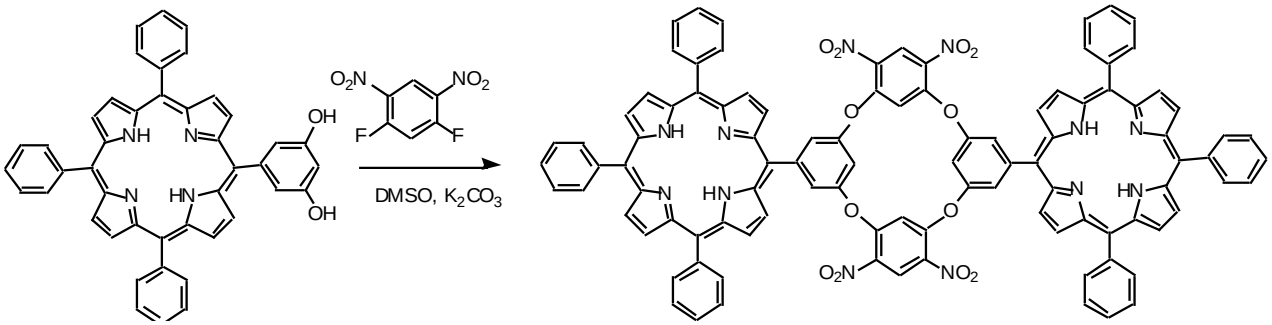


Scheme 5-2: Efficient synthesis of oxacalix[4]arenes and its X-ray structure.

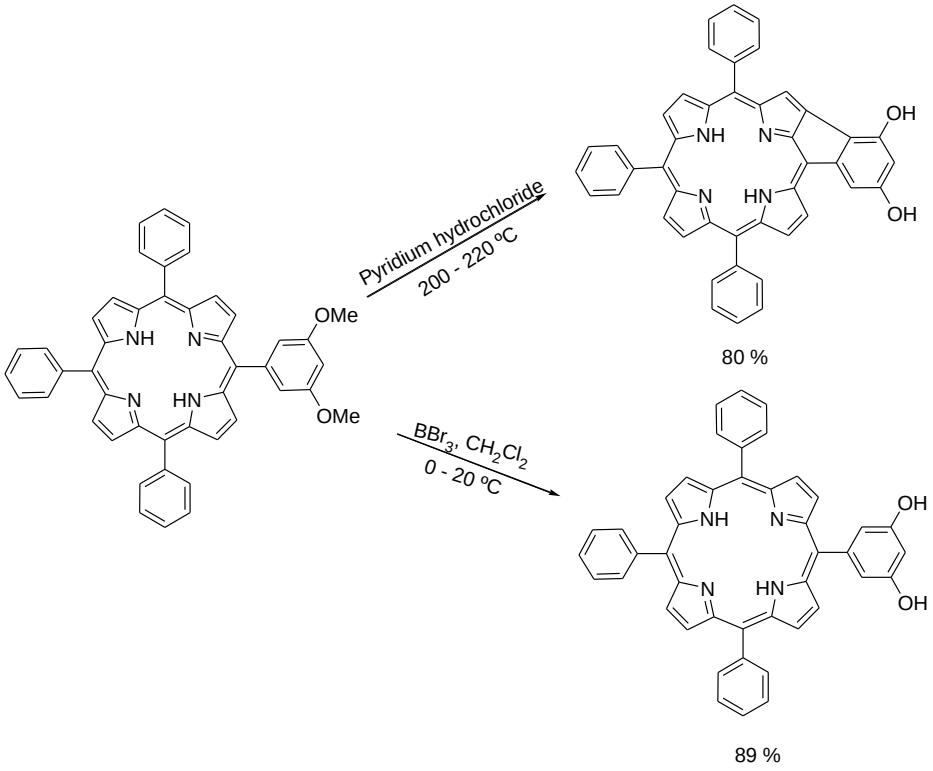
First, a oxacalix[4]arene was synthesized according to Kath's modified conditions[11b]. The reaction proceeded smoothly in 15 minutes at room temperature and gave 93% yield. As expected, X-ray crystallography proved that the oxacalix[4]arene adopts a 1,3-alternating conformation with a 3-4Å separation distance between the two *t*-Bu containing benzene rings. The results gave us confidence that oxacalix[4]arenes can be used as novel spacers.

As shown in *Scheme 5-3*, porphyrin dimer **1** can be easily prepared in 90% yield by simply mixing the same equivalents of compound **4** and **5** with finely-ground K_2CO_3 (<90 μm) in DMSO at room temperature under ambient atmosphere. The reaction was finished in less than 20 minutes and the compound was purified by passing it through a pad of silica gel and eluting with DCM. Remarkably, this synthesis is a one-step procedure and the starting porphyrin **4** can be prepared in multi-gram quantities by mixed aldehyde condensation in propionic acid followed by demethylation with BBr_3 in dichlomethane[15] (*Scheme 5-3*). Unexpectedly, when demethylation was done using pyridium hydrochloride at 200 ℃, an interesting compound **6**, which has a fused five-member ring joining the phenyl *ortho*-position directly to an adjacent β-position was isolated in 84% yield[16]. Porphyrin **6** is believed to be formed via compound **4** and the mechanism is expected to be an acid catalyzed (protonated porphyrin inner nitrogen atoms) intramolecular cyclization (similar to acid catalyzed calixarene formation). A detailed study of this novel reaction to develop a general method to prepare novel π-extended porphyrins is underway.

Interestingly, when granular K_2CO_3 (>250 μm) was used in this reaction, bigger macrocycles **2** and **3** were isolated in addition to **1** (detected by MALDI-TOF MS, see *Figure 5-3*). Flash column separation of the reaction mixture gave a 21% yield of compound **2**, 4% of compound **3**, and 62% of compound **1**.



Scheme 5-3: Synthesis of porphyrin dimer **1.**



Scheme 5-4: Synthesis of 3,5-dihydroxyphenylporphyrins **4** and **6.** Different demethylation conditions resulted in different products.

After an intensive study of the reaction it was found that using granular Na_2CO_3 gave similar yields of these three compounds and highly diluted solution (0.1 mM) also gave similar results. However, when the reaction was done in acetone instead of DMSO, both granular K_2CO_3 and well-ground K_2CO_3 gave compounds **1**, **2** and **3** and the reaction needed longer reaction time (10 hours) to go to completion (disappearance of starting porphyrin by TLC analysis). To the best of our knowledge, compounds **2** and **3** are the first examples of oxacalix[6]arene and oxacalix[8]arene and are also rare examples of heteroatom-bridged calix[6]arenes and calix[8]arenes. Interestingly, when compound **6** reacted with **5** under the same conditions (using granular K_2CO_3), higher yields of bigger macrocycles (27% of oxacalix[6]arene **8** and 15% of oxacalix[8]arene **9** as well as 45% of oxacalix[4]arene **7**) were isolated. Trace amounts of even

bigger macrocycles (oxacalix[10]arene and oxacalix[12]arene) were also detected by MALDI-TOF MS but not isolated due to their very low yields.

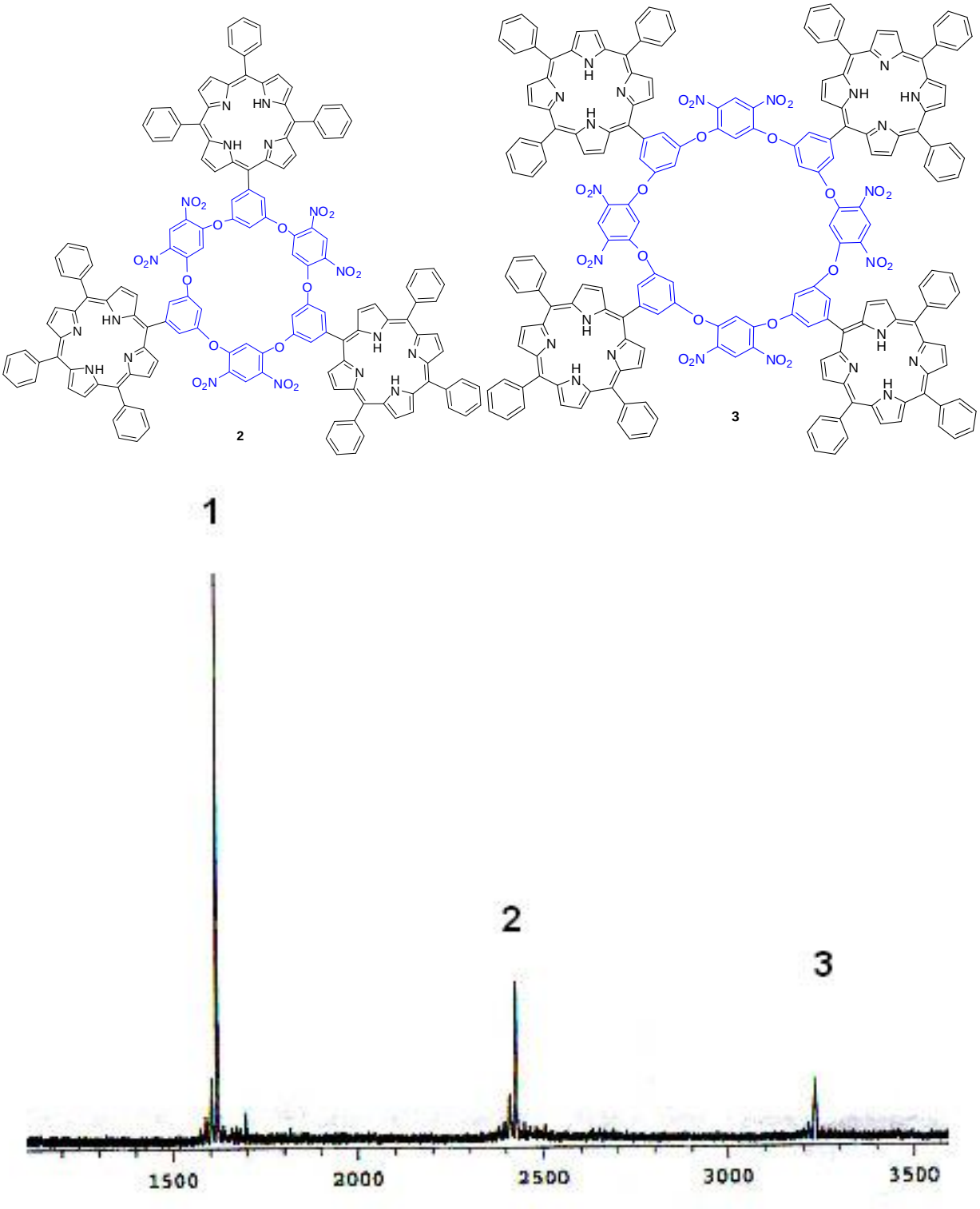


Figure 5-3: MALDI-TOF MS of typical product mixture using granular K_2CO_3 in DMSO.

The formation of the larger macrocyles is normally favored under thermodynamic conditions through co-facial interactions between the pendant porphyrins. Small purple crystals of **1** were grown by slow diffusion of hexane into a DCM solution. *Figure 5-4* shows the molecular structure of **1**. As expected, the oxacalix[4]arene adopts a 1,3-alternating conformation, with the two rings carrying nitro groups forming a dihedral angle of 60.6(2)°, and the two rings carrying porphyrins more nearly parallel, forming a dihedral angle of 8.7(3)°. The two porphyrin ring systems are thus also nearly parallel, forming a dihedral angle of 2.8(7)°. The two porphyrins have a plane-to-plane distance of 3.81 Å but are not perfectly face-to-face, being slipped by 4.11Å, such that the N_4 centroid-N_4 centroid distance is 5.60Å. Thus, they overlap minimally, similar to the manner seen in the special pair of the photoreaction center[17].

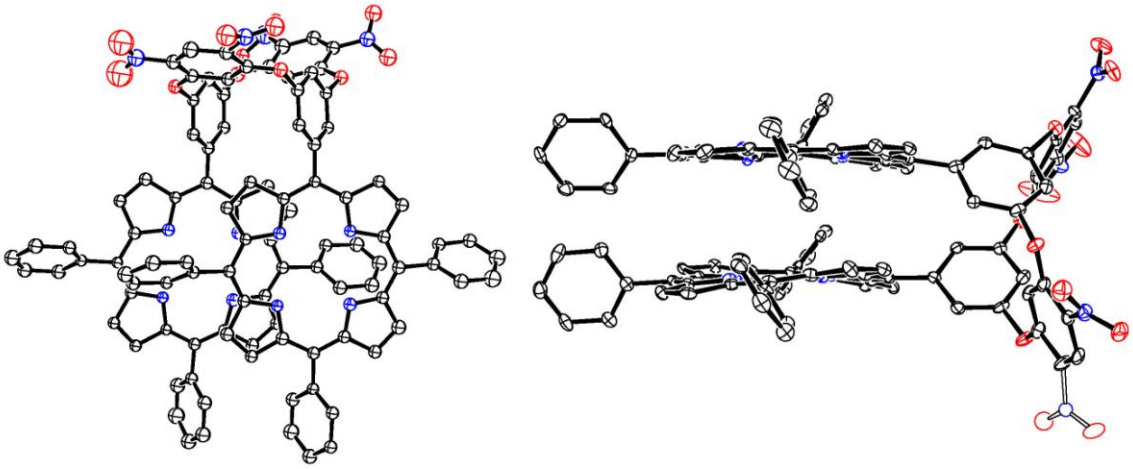
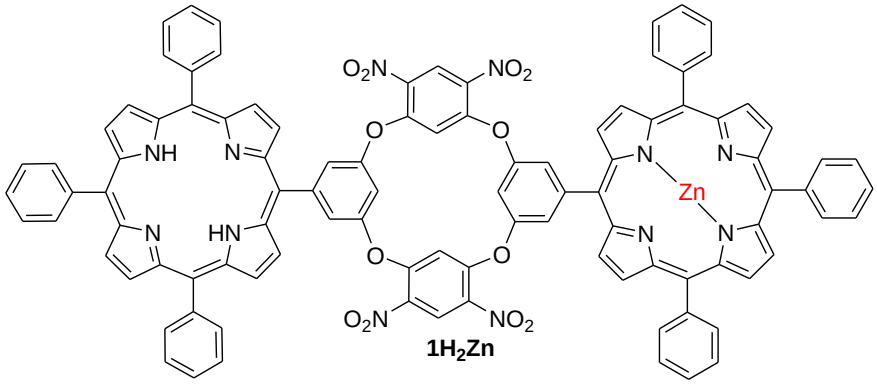


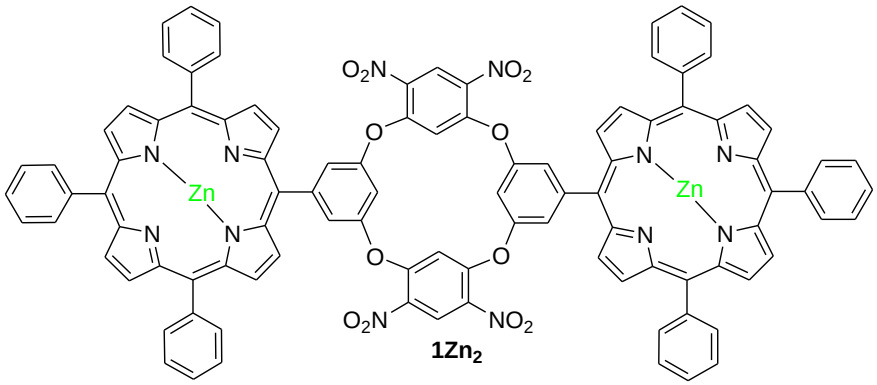
Figure 5-4: Top (left) and side (right) views of X-ray structure of bis-porphyrin **1**.

As can be seen in *Figure 5-4* (side view), the porphyrins are not individually planar but are twisted, showing deviations of up to 0.4Å from their 24-atom average planes. This geometry may be the result of steric hindrance and the electrostatic π-stacking interactions of the two pendant porphyrins. Small purple crystals of **1** were grown by slow diffusion of hexane into DCM solution. However, the AM1 calculated structure of **7** (see *Figure 5-5*) shows that they adopt a face-to-face conformation because of their rigid structures. (The AM1 method was used

to calculate the structure of compound **1**, which fits the experimental crystal structure very well. Therefore, AM1 calculations may also give an accurate structure of compound **7**).



1H$_2$Zn



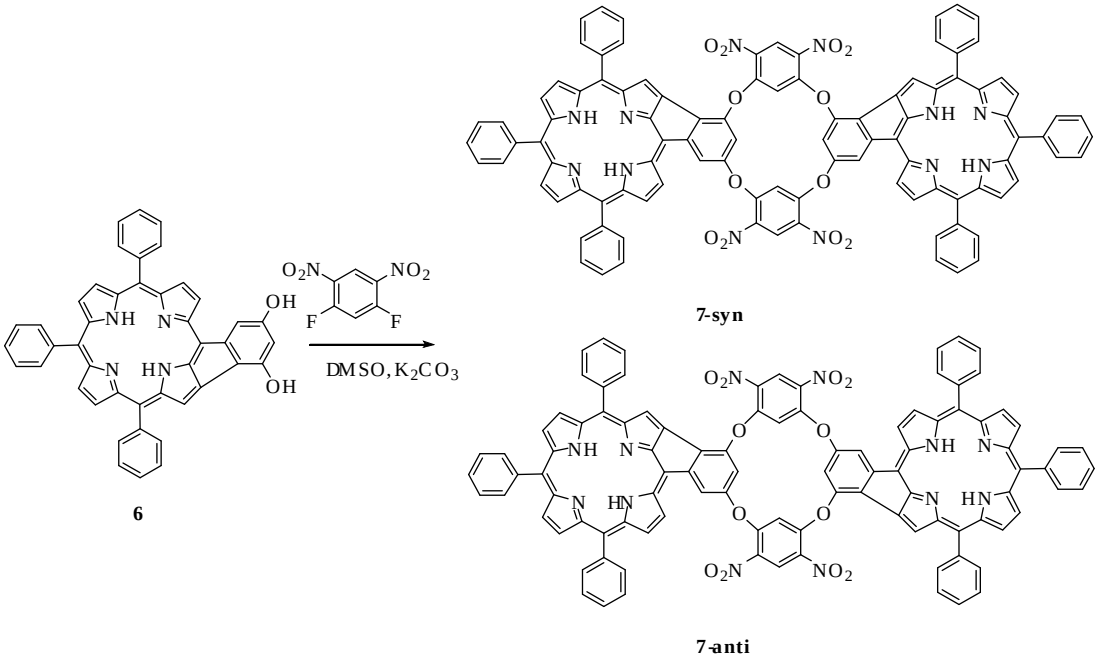
1Zn$_2$

Zinc metal insertions into compounds **1**, **2**, and **3** gave, in quantitative yields, the corresponding **1Zn$_2$**, **2Zn$_3$**, and **3Zn$_4$** complexes. **1H$_2$Zn** was also prepared in 29% yield by monometalation of compound **1** with zinc acetate in dilute solution. It should be noted that this monometalated compound needs careful separation from compounds **1** and **1Zn$_2$**.

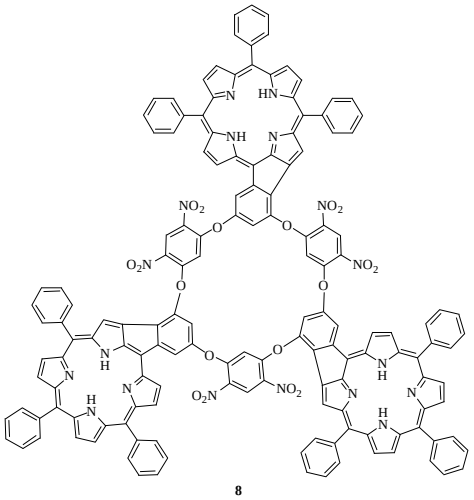
^{1}H-NMR analysis provided information about the structure of **1**, **1H$_2$Zn** and **1Zn$_2$** in solution. The unusual high-field chemical shifts observed for the interior protons on the electrophilic aromatic rings (6.98 ppm for **1**, 6.99 ppm for **1H$_2$Zn** and 7.11 ppm for **1Zn$_2$**) indicate an 1,3-alternating conformation of the oxacalix[4]arenes. However, the ^{1}H-NMR spectra of **1**, **1H$_2$Zn** and **1Zn$_2$** only show half of the expected number of signals for the porphyrin rings, which

indicates that a very rapid (on the NMR time-scale) switching between two conformations is most likely occurring.[18]

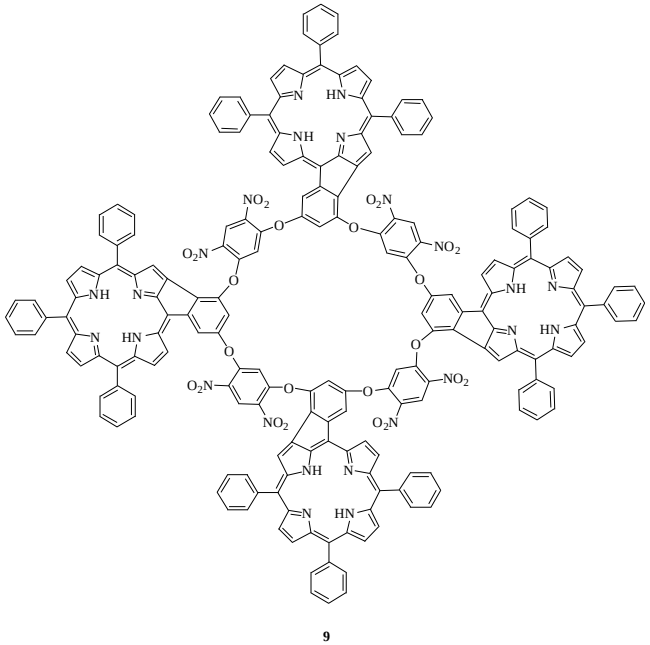
5.3. Prelimary Photophysical Studies



Scheme 5-5: Synthesis of porphyrin dimer **7.**



One possible isomer of **8**



One possible isomer of **9**

The electronic absorption spectrum of **1** (*Figure 5-6*) shows a slightly split Soret band at ~ 406 and 416 nm in THF, while the absorption spectra of **2** and **3** (*Figure 5-7*) show little electronic coupling between the porphyrin rings.

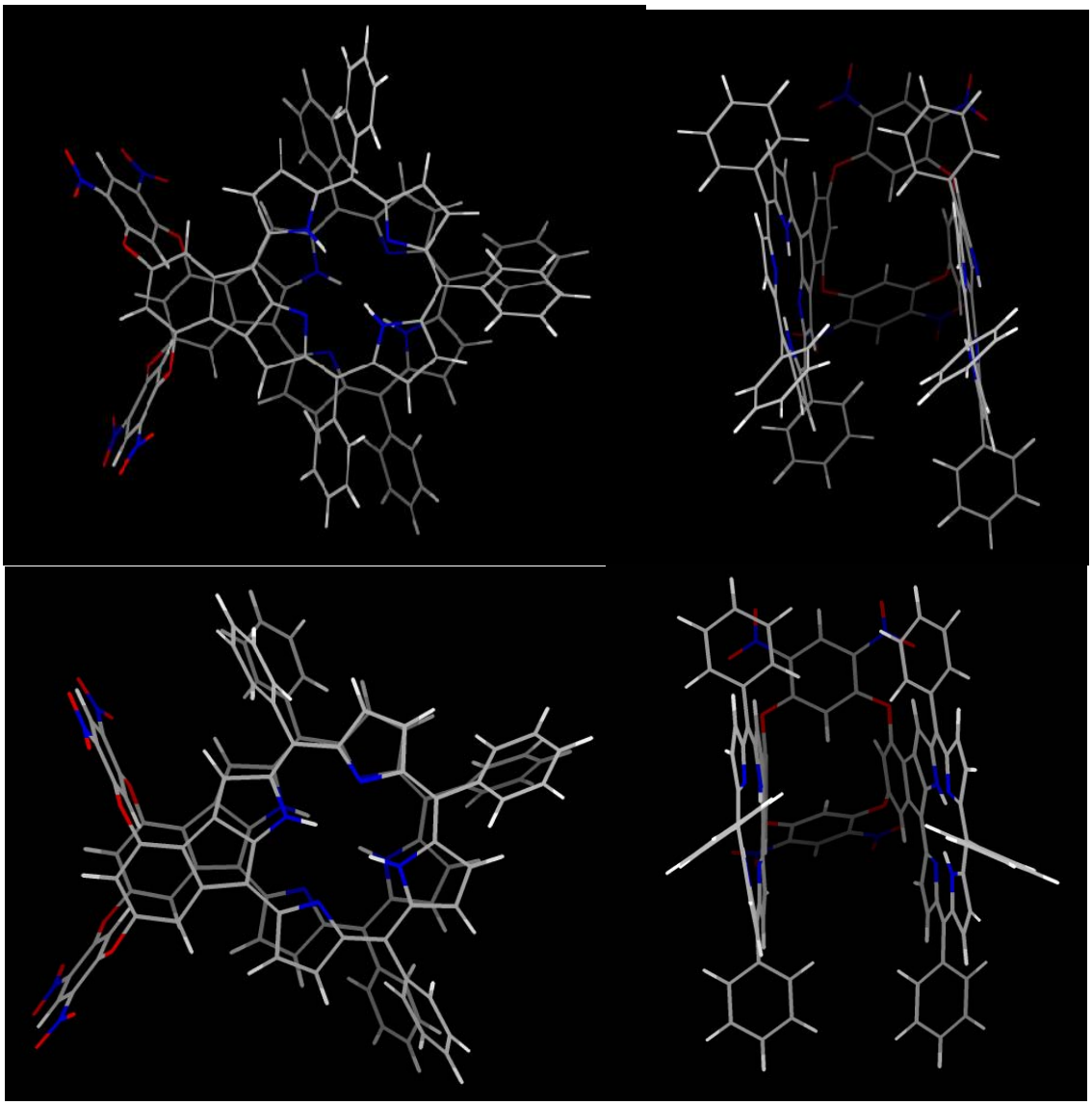


Figure 5-5: The AM1 calculated structure of **7.**

Interestingly, porphyrin **6** shows a triply split Soret band and its oxacalixarenes **7**, **8** and **9** show strong electronic interaction (*Figure 5-8*) due to their more rigid conformations. Compounds **1-3** display strong fluorescence emissions at ~ 650 and 720 nm. However, while **1H$_2$Zn** and **1Zn$_2$** exhibit strong fluorescence, **2Zn$_3$** and **3Zn$_4$** show much weaker emissions

(*Figure 5-9*). Similar fluorescence quenching characteristics were found for the free-base oxacalixarenes **7**, **8** and **9**, and may indicate intermolecular aggregation, for which there is precedent in the literature[12a].

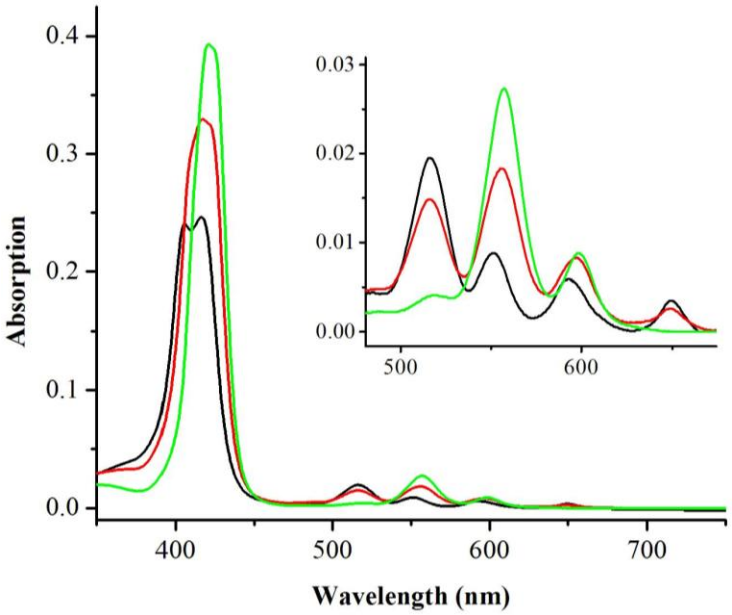


Figure 5-6: UV-vis spectra of compound **1** (black line), **1-H_2Zn** (red line), and **1-Zn_2** (green line), in THF solution at the concentration of 1.0×10^{-6} M at room temperature.

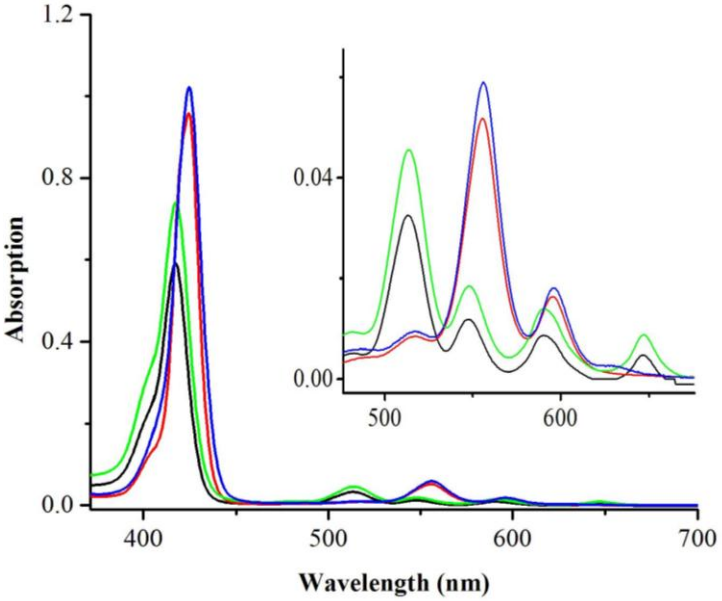


Figure 5-7: UV-vis spectra of compound **2** (black line), **3** (green line)**, 2-Zn_3** (red line), and **3-Zn_4** (blue line), in THF solution at the concentration of 1.0×10^{-6} M at room temperature.

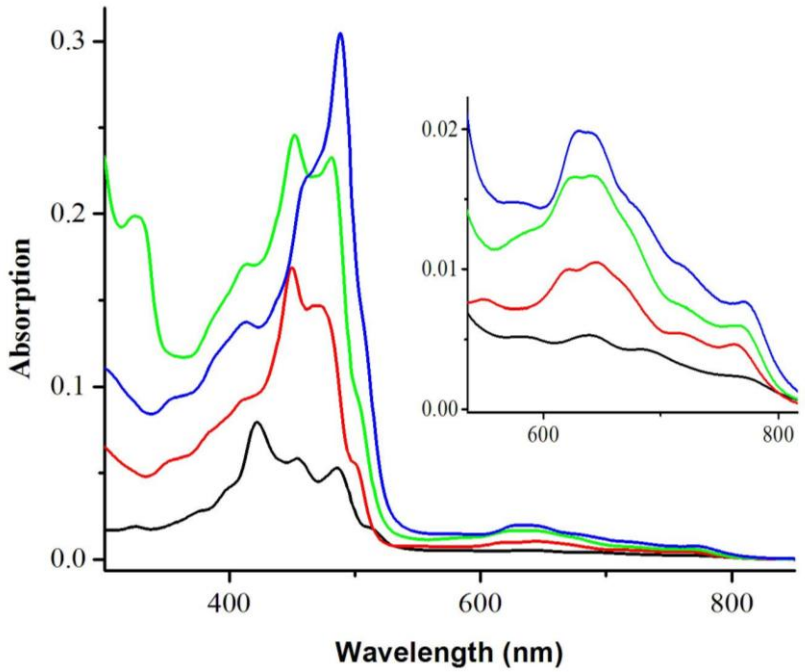


Figure 5-8: UV-vis spectra of compound **6** (black line), **7** (red line)**, 8** (green line), and **9** (blue line), in DCM solution at the concentration of 1.0×10^{-6} M at room temperature.

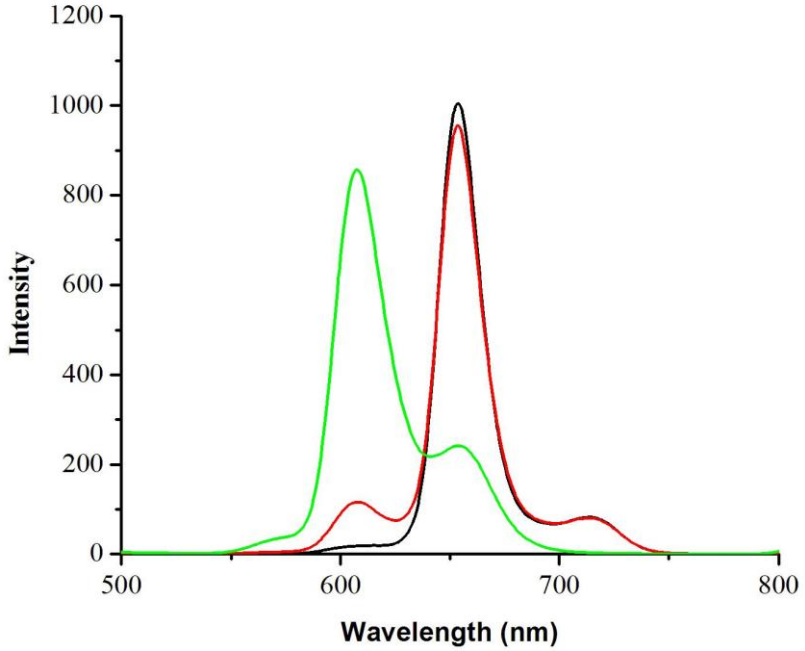


Figure 5-9: Fluorescence spectra of compound **1** (black line), **1-H_2Zn** (red line), and **1-Zn_2** (green line), in THF solution at the concentration of 1.0×10^{-6} M at room temperature.

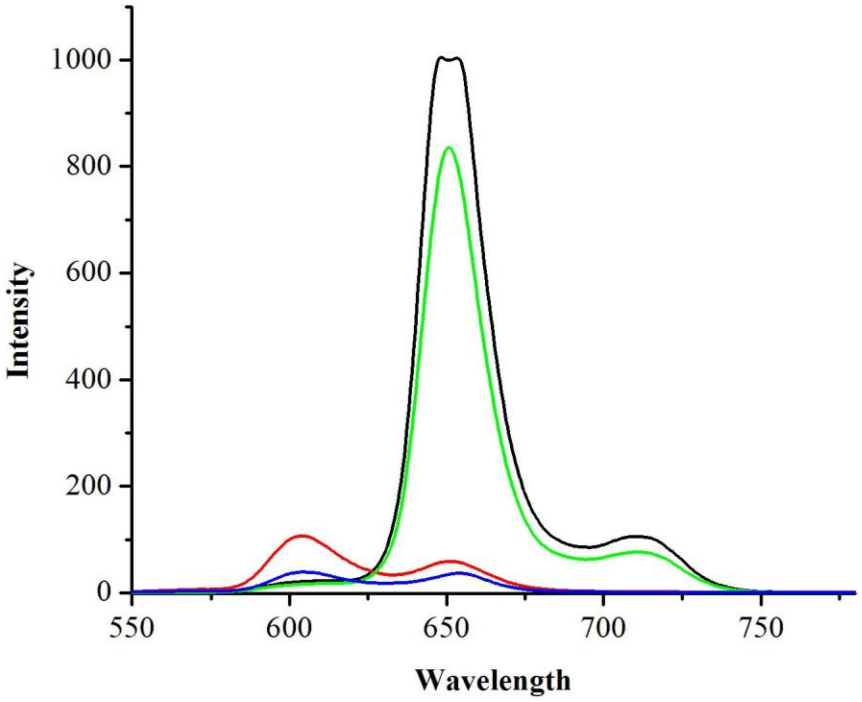


Figure 5-10: Fluorescence spectra of compound **2** (black line), **3** (green line), **2-Zn$_3$** (red line), and **3-Zn$_4$** (blue line), in THF solution at the concentration of 1.0×10^{-6} M at room temperature.

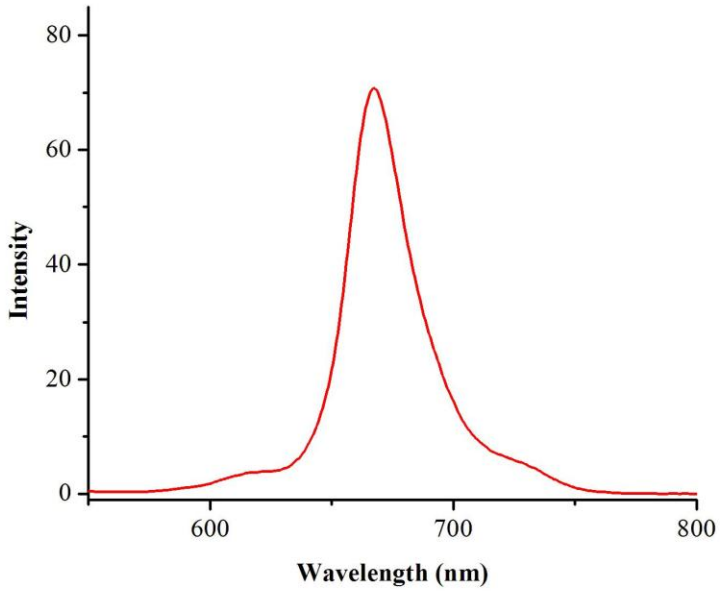
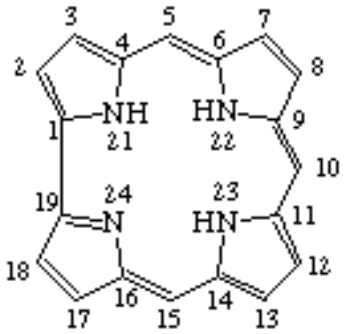


Figure 5-11: Fluorescence spectra of compound **6** in THF solution at the concentration of 1.0×10^{-6} M at room temperature.

In conclusion, oxacalixarene-bis-porphyrins and higher oligomers can be synthesized in a single step, in high yields. This methodology is general for the preparation of a variety of cofacial multiporphyrin architectures, which will find applications in the area of multielectron redox catalysis and energy transfer. We are currently studying the conformations of large oxacalixarene-porphyrins, investigating their intriguing photophysical properties and exploring their host-guest chemistry.

5.4. Oxacalix[4]arenes Linked Corroles and Porphyrin-Corroles

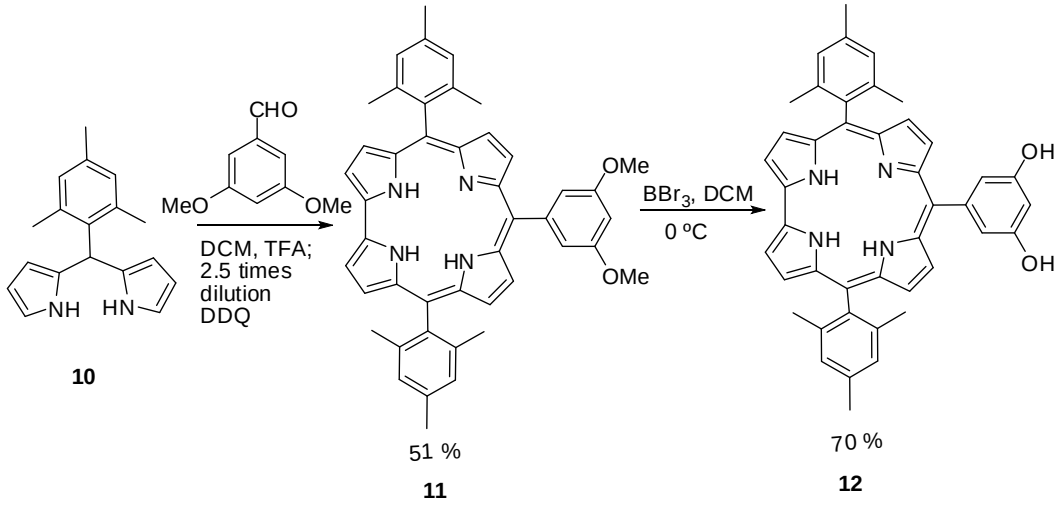
Next we turned our attention to the synthesis of corrole-containing supramolecules. The carbon skeleton of corrole is the same as found in the core of vitamin B_{12} (the corrin ring). The ring consists of nineteen carbon atoms, with four nitrogen atoms in the core of the molecule. Corrole is a porphyrin-like 18-π aromatic macrocycle except for one direct pyrrole-pyrrole linkage, which displays a unique ability to stabilize unusually high valence state transition metals because corrole normally serves as a trianionic ligand with transition metals; on the other hand, porphyrins are dianionic.



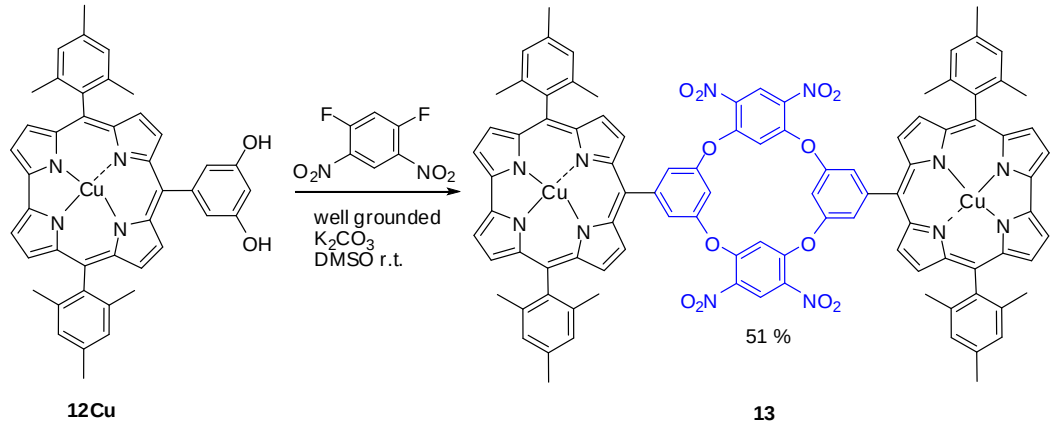
The research on corrole is much less developed comparing with porphyrins because of the limited development of synthetic procedures[19]. Total syntheses of β-substituted corroles have been accomplished through different approaches but all need multiple steps[20]. Meso-triphenylcorroles were very hard to synthesize even only a few years ago. However, with the

breakthrough of corrole synthesis starting from 1999, research on corroles has been increased dramatically[21]. Several groups deserve the credit for improving the syntheses of corrles: early on it was the Smith group[22] and then Gross's group[23], and recently Gryko's group[24]. Especially, the Gryko's method which is modified Lindsey's condition provides the efficient method to access trans-A_2B corroles.

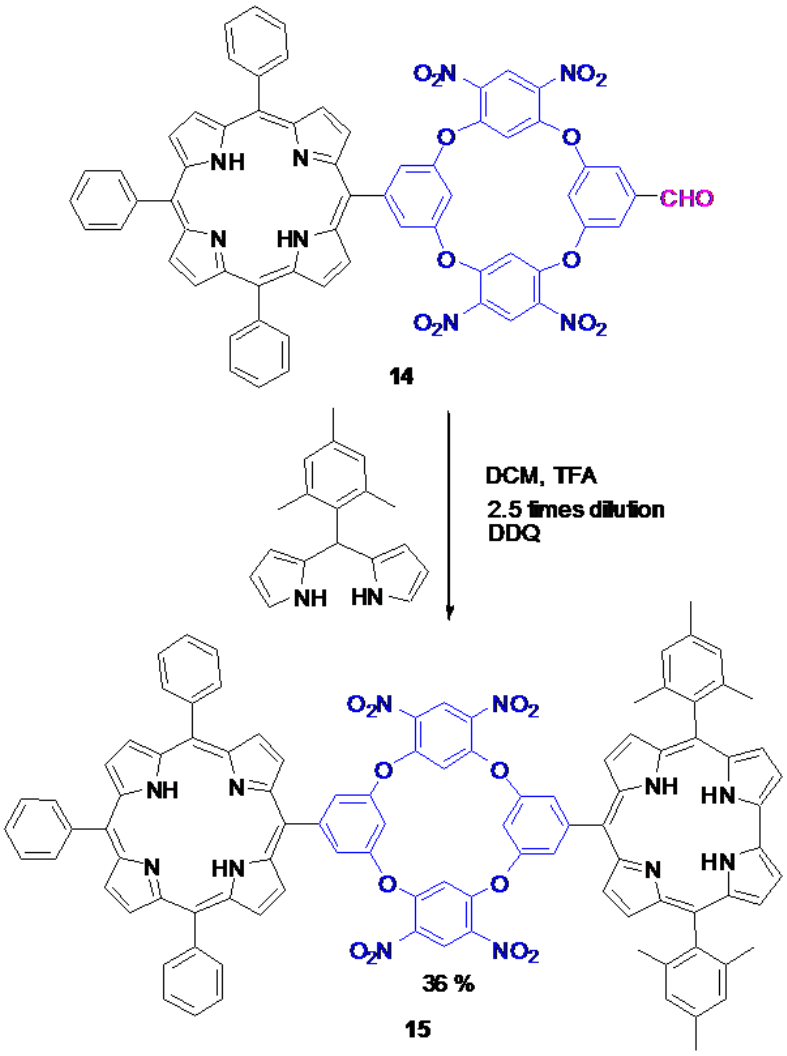
Here, the preliminary results of our efforts to build the corrole dimers and trimers are presented. Although corrole dimers have been constructed by several groups[25,26], the field is still very limited.



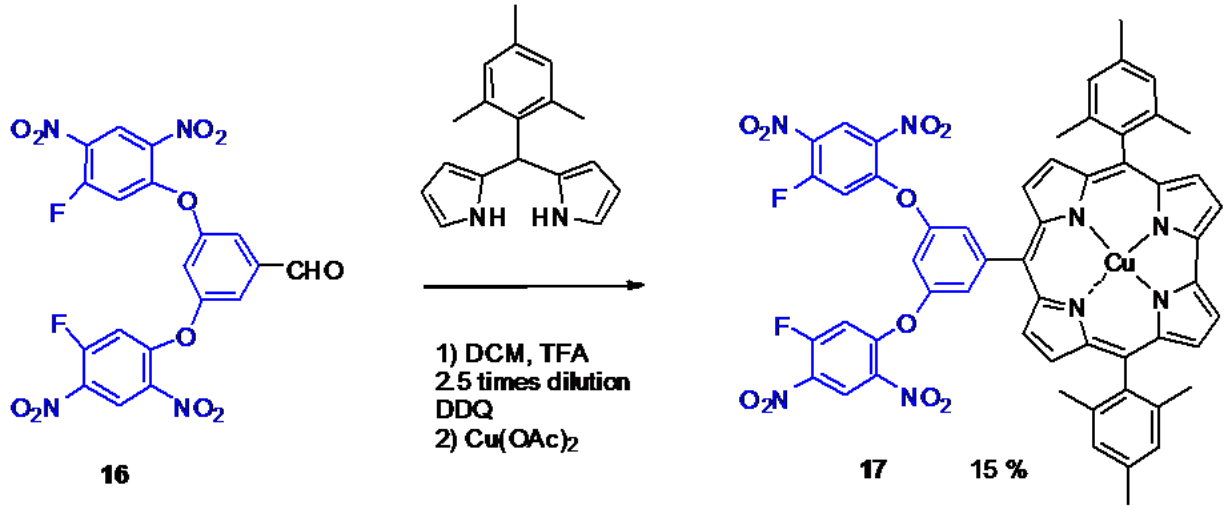
Scheme 5-5: Synthesis of 3,5-dihydroxylphenylcorrole.



Scheme 5-6: Synthesis of oxacalix[4]arene linked bis-(copper corrole).



Scheme 5-7: Synthesis of oxacalix[4]arene linked compound **15.**

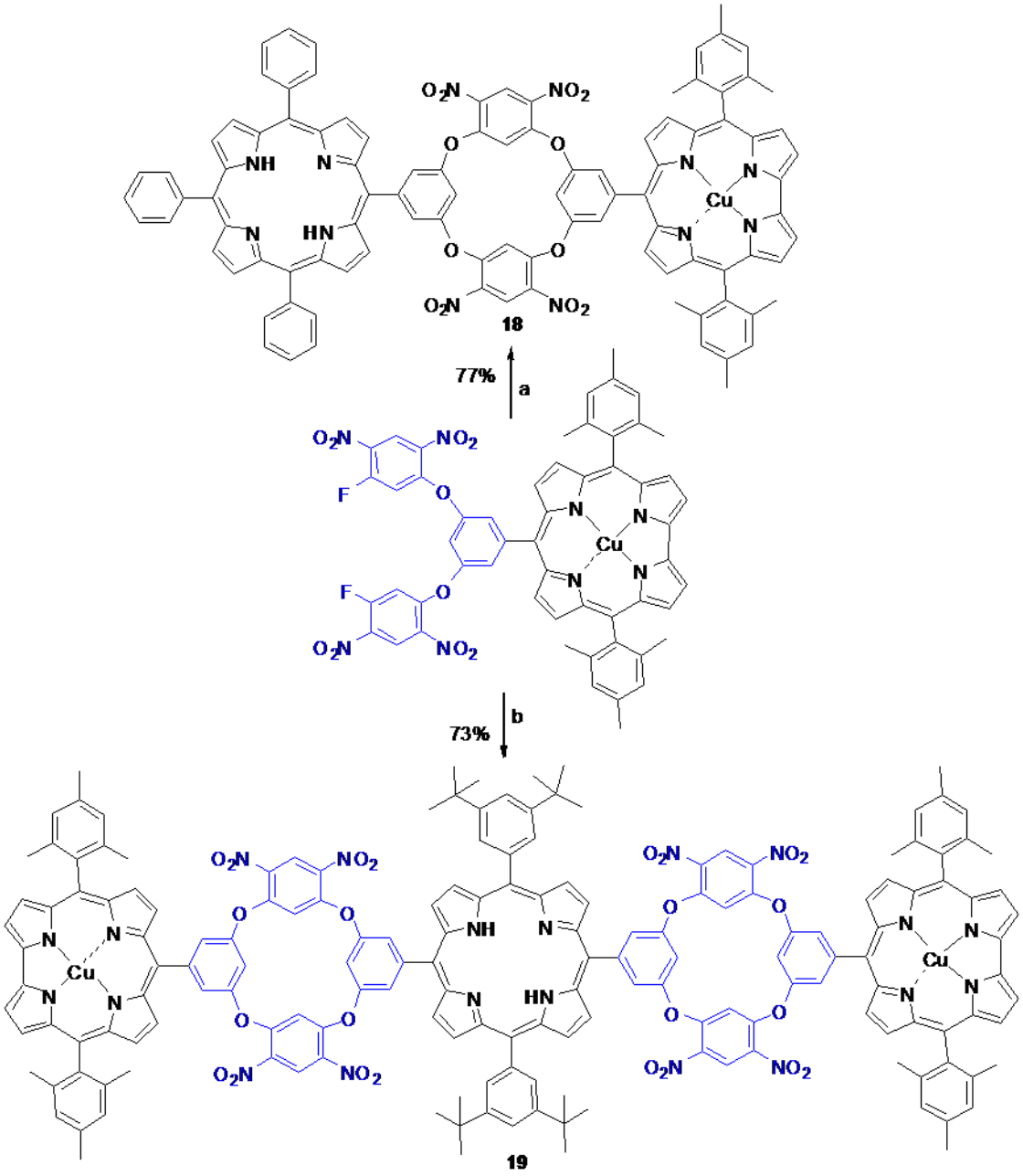


Scheme 5-8: Synthesis of oxacalix[4]arene linked corrole **17**.

As shown in *Scheme 5-5*, dipyrromethane **10** was prepared in 50% yield using $MgBr_2$ as Lewis acid in excess pyrrole (50 equiv)[27]. This compound was selected because sterically hindered dipyrromethanes normally give high yields of corrole using the Gryko method[25]. As shown in *Scheme 5-5*, the resulting corrole **11** was isolated in good yield (51%) as a purple solid, which is a characteristic color for this type of corrole (most corroles are green). The corrole **11** is relatively stable but can slowly decompose in light and oxygen. Demethylation of **11** gave **12** in 70% yield using BBr_3 in DCM in the dark. A small amount of byproduct was identified as brominated corrole. Copper insertion into corrole **11** gave **11Cu** in almost quantitative yield using $Cu(acac)_2$ in a mixture of chloform and methanol (3:1). **11Cu** was much more stable than **11**. However, demethylation of **11Cu** resulted in the free base **12** as well as the corresponding brominated corroles in quite large percentage. It seemed that BBr_3 is strong enough to remove copper metal from the corresponding corrole. So demethylation of the corrole was performed with caution; control of temperature and amount of BBr_3 are important. Separation of the copper containing corrole from the corresponding brominated corroles is much difficult than the free base. Insertion of copper using the same method as for **11Cu** gave **12Cu** in quantitative yield. In *Scheme 5-6*, the oxacalix[4]arene linked bis-(copper corrole) was prepared using a similar method as for compound **1**. The reaction gave 51% of the target as well as some polar material.

Next, we turned our attention to building unsymmetrical oxacalix[4]arenas, as demonstrated by our recent "hangman" porphyrin project[28]. Starting from porphyrin **14**[28], compound **15** was isolated in 35% yield (*Scheme 5-7*). The method is straightforward and the target porphyrin-corrole dimer was isolated by silica gel column chromatography, along with some unreacted compound **14**. Another approach which was used to build the supramolecular system is shown in *Schemes 5-8* and *5-9*. Linear trimer **16**[28] was used to prepare corrole **17** in 15% yield after direct

copper insertion following the reaction. Corrole **17**, although obtained in low yield, is quite easy to purify and synthesize in large amount. Corrole **17** proved to be a valuable precursor. Mixing equimolar proportions of **17** and porphyrin **4** under K_2CO_3 in DMSO gave compound **18** in 77% yield after separation on a silica gel column.



Scheme 5-8: Synthesis of oxacalix[4]arene linked compounds **18** and **19**; Reaction conditions: a) porphyrin **4** and K_2CO_3; b) 5,15-(3,5-dihydroxyphenyl)-10,20-(3,5-ditertbutylphenyl)porphyrin and K_2CO_3.

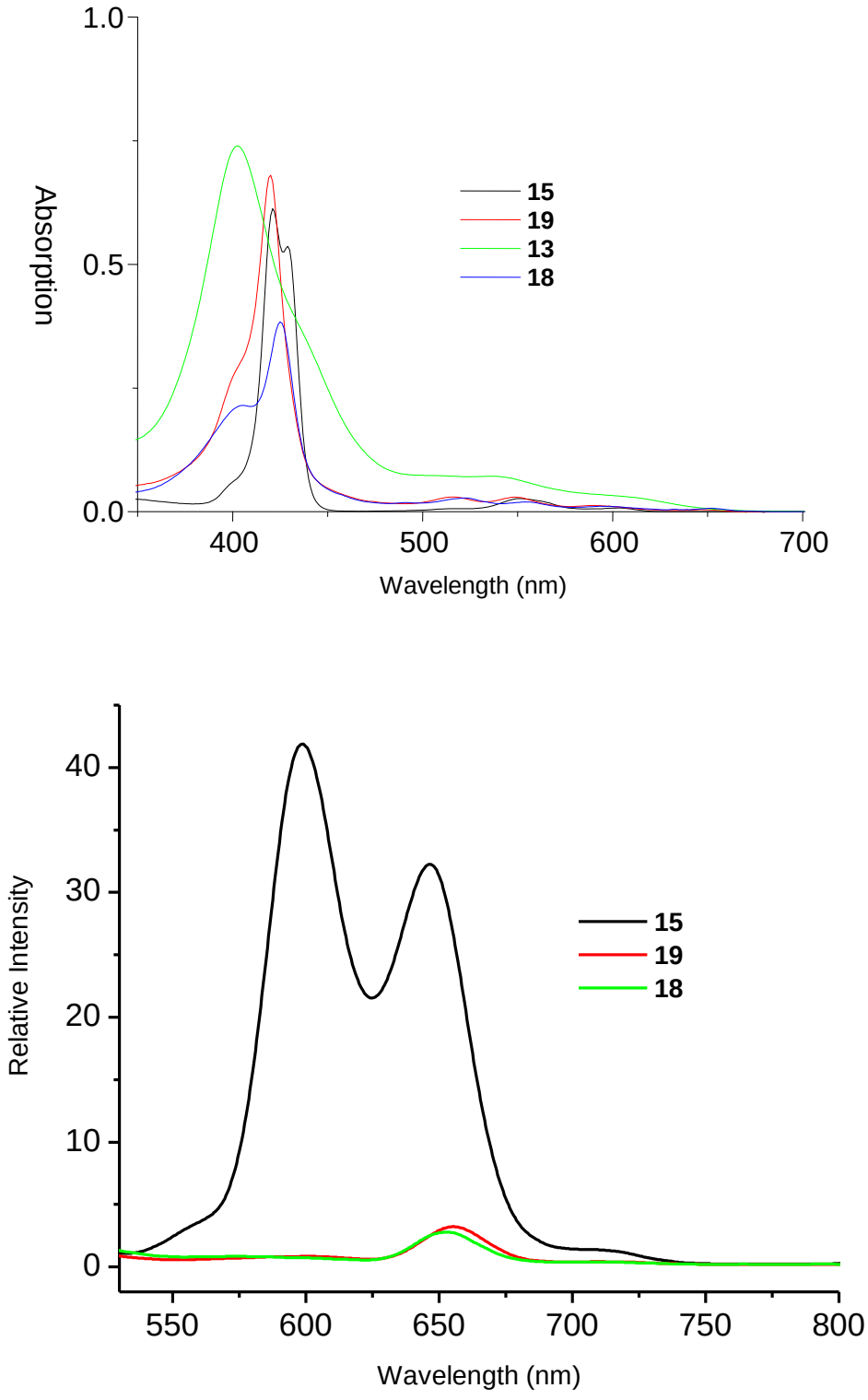


Figure 5-12: UV-vis (top) and Fluorescence (bottom, exited at 420 nm) spectra of oxcalix[4]arene linked corroles in DCM.

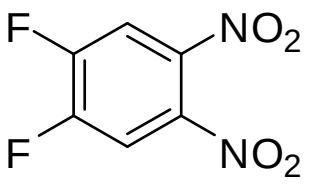
The reaction was very fast and efficient. In a similar manner, simply changing the ratio (to 1:2) of 5,15-(3,5-dihydroxyphenyl)-10,20-(3,5-ditertbutylphenyl)porphyrin ($TPPOH_4$) and compound **17** gave the corresponding compound **19** in 73% yield.

MALDI-TOF MS was a good tool to follow the reaction and identify the products. All compounds showed the expected mass peaks using MALDI-TOF MS. UV-vis of porphyrin-corroles gave the combination of corrole and porphyrin, which may indicate the macrocycles' weak interactions. The copper complex of the corrole did not show fluorescence while the free base corrole showed high fluorescence, as expected. The porphyrin-copper corrole complex showed very weak fluorescence from the porphyrin part, which was quenched by copper corrole species *(Table 5-1*).

Table 5-1: Photophysical Data in Degassed DCM at Room Temperature.

Compounds	**13**	**15**	**18**	**19**	**4**	**12**	**$TPPOH_4$**
Fluorescence[a] quantum yield (DCM)	NA	0.08	0.01	0.005	0.10	0.28	0.14

a: excitation at 420 nm, TPP as Standard.



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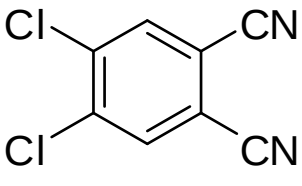
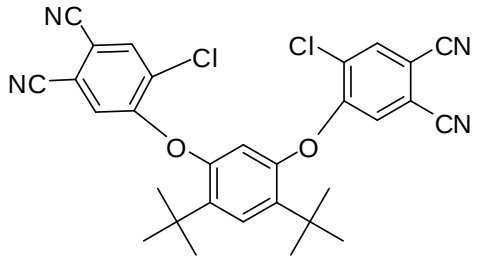


21

Attempts to extend the method, using electrophile **20**, to build analogs of cyclic ethers were not successful so far. Analogs of dimer **1** based on compound **20** would be expected to have larger distance due to the geometry of the cyclic ether. However, the reaction of **20** with

porphyrin **4** generated a complex mixture from which MALDI MS indicated the target was indeed formed, but along with many of bigger macrocycles. Separation was not possible for the reaction mixture. Meanwhile, compound **21** was found to be insufficiently reactive to give high yields of the cyclic ethers, although increasing the temperature of the reaction to 100 ℃ gave a mixture of the expected dimer, trimer, and tetramers, as well as the corresponding open chain mixtures as judged by MALDI MS. Once again, separation was difficult. A test experiment using 4,6-di-tert-butylbenzene-1,3-diol also gave incomplete reactions. Compound **22** was isolated as evidence of the incomplete reactions. *Figure 5-13* showed the X-ray structure of compound **22**.



22

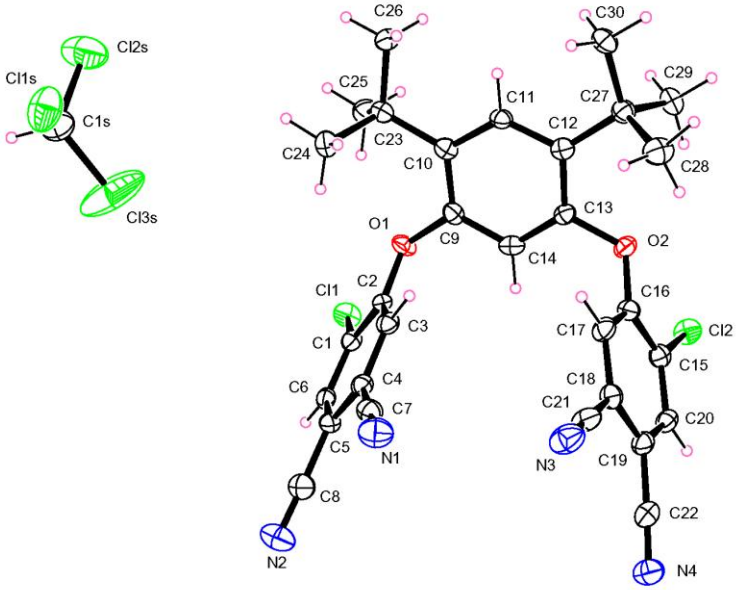


Figure 5-13: Molecular structure and X-ray structure of compound **22**.

5.5. Experimental

Instrumentation and Materials

All reactions were monitored by TLC using 0.25 mm silica gel plates with or without UV indicator (60F-254). Silica gel (Sorbent Technologies 32-63 μm) was used for flash column chromatography. ^{1}H- and ^{13}C-NMR were obtained on either a DPX-250 or an ARX-300 Bruker spectrometer. Chemical shifts (δ) are given in ppm relative to $CDCl_3$ (7.26 ppm, ^{1}H), THF (3.58 ppm, ^{1}H) or DMSO (1.73 ppm, ^{1}H) unless otherwise indicated. Electronic absorption spectra were measured on a Perkin Elmer Lambda 35 UV-Vis spectrophotometer and fluorescence spectra were measured on a Perkin Elmer LS55 spectrometer. MALDI-TOF mass spectra were obtained on an Applied Biosystems QSTAR XL, using the positive method with dithranol as matrix unless otherwise indicated. All solvents were obtained from Fisher Scientific (HPLC grade, Houston, TX) and were used without further purification. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

General Procedures and Compound Data

Synthesis of compound 3,5-dimethoxyphenyl-5,10,15-triphenylporphyrin and demethylation to give **4** were done as described in Chapter 1. Other known compounds are synthesized according to the original literature.

Synthesis of Oxacalixarenes 1: 59.0 mg (0.09 mmol) of compound **4**, 1,5-difluoro-2,4-dinitrobenzene (18.6 mg, 0.09 mmol) and 50.4 mg of finely ground anhydrous K_2CO_3 (0.36 mmol) were combined into 50 mL round bottom flask. 10 mL of DMSO was added to the reaction mixture and it was stirred vigorously for 1 h at room temperature under ambient atmosphere. The reaction mixture was then partitioned between EtOAc (100 mL) and brine (100 mL). The resulting mixture was separated and the aqueous layer was extracted until colorless.

The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified using a pad of silica gel using DCM as eluting solvent. The only major fraction was collected, concentrated and recrystallized from DCM and hexane. The purple solid was dried under vacuum, giving target compound **1** 67.1 mg (90.5% yield). HRMALDI-TOF $[M+H]^+$ Calcd. for $C_{100}H_{61}N_{12}O_{12}$ 1622.4563, found 1622.4569. Anal. Calcd. for $C_{100}H_{60}N_{12}O_{12}.2H_2O$: C, 72.46; H, 3.89; N, 10.14. Found: C, 72.39; H, 3.94; N, 9.98. ^{1}H-NMR ($CDCl_3$) 9.09 (s, 2H, phenyl-H), 8.60-8.91 (b, 16H, phenyl-H), 8.30 (d, 8H, β-H), 8.25 (m, 4H, β-H), 8.23 (m, 4H, β-H), 7.80 (m, 18H, phenyl-H), 7.53 (s, 2H, p-phenyl-H), 6.98 (s, 2H, phenyl-H), -3.20 (s, 4H, NH). UV-vis (THF): λ_{max} (log ε) 406 (5.4), 416 (5.4), 516 (4.2), 551 (3.9), 593 (3.8), 650 (3.5) nm.

Synthesis of Oxacalixarenes 2 and 3: The syntheses of bigger macrocycles **2** and **3** were similar to the synthesis of **1** except using granular K_2CO_3 (>250 μm) instead of finely ground K_2CO_3 (<80 μm). 59.1 mg (0.09 mmol) of compound **4**, 1,5-difluoro-2,4-dinitrobenzene (18.6 mg, 0.09 mmol) and 51.0 mg of granular anhydrous K_2CO_3 (0.36 mmol) were combined in a 20 mL vial. 10 mL DMSO was added and the reaction mixture was stirred for 3 h at room temperature under ambient atmosphere. Workup was the same as with synthesis of **1**. Purification on a silica gel column gave three fractions: firstly, compound **2** was eluted using DCM/hexane = 5/1; then compound **3** was eluted; finally, compound **1** was eluted using DCM. Recrystallization from DCM/hexane and solvent removal under vacuum gave a 21% yield of compound **2**, 4% of compound **3** and 62 % of compound **1**. Compound **2**: HRMALDI-TOF Calcd. for $C_{150}H_{90}N_{18}O_{18}$ 2431.6712, found m/z 2431.6808. Anal. Calcd. for $C_{150}H_{90}N_{18}O_{18}.2H_2O$: C, 72.98; H, 3.84; N, 10.21. Found: C, 72.80; H, 3.75; N, 10.09. UV-vis (THF): λ_{max} (log ε) 417 (5.8), 514 (4.5), 547 (4.1), 590 (3.9), 647 (3.7) nm. Compound **3**:

HRMALDI-TOF Calcd. for $C_{200}H_{120}N_{24}O_{24}$ 3242.8970, found m/z 3242.9056. Anal. Calcd. for $C_{200}H_{120}N_{24}O_{24}.H_2O$: C, 73.66; H, 3.77; N, 10.31. Found: C, 73.70; H, 3.88; N, 10.12. UV-vis (THF): λ_{max} (log ε) 417 (6.0), 514 (4.7), 548 (4.3), 591 (4.1), 647 (3.9) nm.

Zinc Complexes - $1Zn_2$, $2Zn_3$ and $3Zn_4$: Zinc insertion into **1**, **2** and **3** was accomplished in a refluxing mixture of chloroform and methanol (v/v = 9/1) using excess $Zn(OAc)_2$. The mixture was filtered to remove inorganic salts, and the filtrate was evaporated and passed through a pad of silica gel using DCM for elution. These reactions gave quantitative yields.

$1Zn_2$: HRMALDI-TOF Calcd. for $C_{100}H_{56}N_{12}O_{12}Zn_2$ 1748.2717, found m/z 1748.2728. Anal. Calcd. for $C_{100}H_{56}N_{12}O_{12}Zn_2.2CH_3OH$: C, 67.59; H, 3.56; N, 9.28. Found: C, 67.65; H, 3.61; N, 9.14. UV-vis (THF): λ_{max} (log ε) 421 (5.6), 557 (4.4), 598 (3.9) nm. ^{1}H-NMR (THF-d_8): 9.06 (s, 2H, phenyl-H), 8.71 (b, 16H, phenyl-H), 8.41 (m, 8H, β-H), 8.23 (m, 8H, β-H), 7.83 (s, 2H, phenyl-H), 7.78 (m, 18H, phenyl-H), 7.11 (s, 2H, phenyl-H).

$2Zn_3$: HRMALDI-TOF Calcd. for $C_{150}H_{84}N_{18}O_{18}\,Zn_3$ 2622.4087, found m/z 2622.4318. Anal. Calcd. for $C_{150}H_{84}N_{18}O_{18}.CH_2Cl_2$: C, 66.98; H, 3.20; N, 9.30. Found: C, 66.75; H, 3.45; N, 8.85. UV-vis λ_{max} (log ε) (THF): 424 (5.8), 556 (4.7), 595 (4.2) nm. ^{1}H-NMR (THF-d_8): 9.03 (s, 3H, phenyl-H), 8.95 (d, 6H, J = 4.5 Hz, β-H), 8.76 (d, 6H, J = 4.6 Hz, β-H), 8.69 (d, 12H, J = 3.5 Hz, β-H), 8.12 (m, 6H, phenyl-H), 8.02 (s, 6H, phenyl-H), 7.92 (b, 12H, phenyl-H), 7.87 (s, 3H, phenyl-H), 7.72 (m, 9H, phenyl-H), 7.69 (s, 3H, phenyl-H), 7.40 (s, 18H, phenyl-H).

$3Zn_4$: HRMALDI-TOF Calcd. for $C_{200}H_{113}N_{24}O_{24}Zn_4$ 3497.5527, found m/z 3497.5495. Anal. Calcd. for $C_{200}H_{112}N_{24}O_{24}Zn_4.CHCl_3.H_2O$: C, 66.43; H, 3.19; N, 9.25. Found: C, 66.07; H, 3.42; N, 9.00. UV-vis (THF): λ_{max} (log ε) 425 (6.0), 556 (4.8), 596 (4.3) nm. ^{1}H-NMR (THF-d_8): 8.83 (s, 4H, phenyl-H), 8.70 (m, 16H, β-H), 8.58 (m, 16H, β-H), 8.09 (m, 8H, phenyl-H), 7.90 (s, 8H,

phenyl-H), 7.69 (m, 16H, phenyl-H), 7.59 (s, 4H, phenyl-H), 7.46 (s, 4H, phenyl-H), 7.37 (m, 12H, phenyl-H), 7.22 (b, 18H, phenyl-H).

Monometalated Complex - $1H_2Zn$: 28.2 mg of compound **1** was dissolved in 80 mL DCM in a 200 mL round bottom flask. The solution was refluxed and then 4.8 mg $Zn(OAc)_2$ in 10 mL of methanol was added dropwise to the refluxing solution during the course of 1 h. The mixture was refluxed and the reaction was monitored by TLC (the order R_f value: **1** > **$1H_2Zn$** > **$1Zn_2$**). About 4 h later, the reaction was stopped and the solvents were removed. The residue was purified by column chromatography on silica gel using DCM/hexane (v/v = 9/1) as eluting solvents; the second band was collected. Recrystallization from DCM/hexane and solvent removal under vacuum gave a 29% yield of compound **1-H_2Zn.** HRMALDI-TOF Calcd. for $C_{100}H_{59}N_{12}O_{12}Zn$ 1685.3688, found m/z 1685.3734. Anal. Calcd. for $C_{100}H_{58}N_{12}O_{12}Zn.2CH_3OH$: C, 70.04; H, 3.80; N, 9.60. Found: C, 70.02; H, 3.61; N, 9.29. UV-vis (THF): λ_{max} (log ε) 417 (5.5), 516 (3.6), 556 (4.3), 597 (3.9), 648 (3.4) nm. ^{1}H-NMR (THF-d_8): 10.86 (s, 1H, phenyl-H), 9.13 (s, 1H, phenyl-H), 9.06 (s, 1H, phenyl-H), 8.67 (b, 16H, phenyl-H), 8.43 (m, 8H, β-H), 8.24 (m, 8H, β-H), 7.89 (s, 1H, phenyl-H), 7.80(m, 18H, phenyl-H), 6.99 (s, 2H, phenyl-H).

Synthesis of Compound 6: Compound **10** (199 mg) and 5 g of pyridium hydrochloride were mixed together in a 50 mL round bottom flask in a 220 ℃ oil bath. When the pyridium hydrochloride was melted (at 170 ℃), the solution turned green in color. After 2 h, TLC indicated a major green spot which was compound **6** and a minor purple spot right before **6** which is compound **4**. After the solution was stirred for 4 h, compound **4** had disappeared from the TLC. The reaction was stopped and the mixture was poured into 200 mL of cold water. 200 mL EtOAc was added and the resulting mixture was separated. The aqueous layer was extracted until colorless with EtOAc. The combined organic layer was washed with 0.1 M HCl solution

twice and then washed with saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel using a 1:1 mixture of chloroform and EtOAc. The major fraction was collected, concentrated, and recrystallized from DCM/hexane. The residue was dried under vacuum, giving compound **6** (160 mg, 84 % yield). ^{1}H-NMR (DMSO-d_6) 9.92 (s, 1H, OH), 9.77 (s, 1H, OH), 9.22 (d, 1H, J = 4.3 Hz, β-H), 8.54 (d, 1H, J = 4.9 Hz, β-H), 8.28 (d, 1H, J = 3.6 Hz, β-H), 8.24 (d, 1H, J = 3.6 Hz, β-H), 8.16 (d, 1H, J = 4.4 Hz, β-H), 8.12 (d, 1H, J = 4.5 Hz, β-H), 8.03 (m, 6H, phenyl-H), 7.78 (m, 9H, phenyl-H), 7.22 (s, 1H, dihydroxyphenyl-H), 7.08 (s, 1H, dihydroxyphenyl-H). UV-vis (DCM): λ_{max} (log ε) 422 (4.9), 455 (4.8), 486 (4.7), 583 (3.7), 640 (3.7), 683 (3.6) nm. MALDI-TOF: $[M+H]^+$ 645.5, HR-MALDI-TOF Calcd. for $C_{44}H_{28}N_4O_2$ 645.2290, found 645.2272.

Synthesis of Oxacalixarenes 7, 8 and 9: The syntheses of **7**, **8** and **9** were similar to the syntheses of **2** and **3** but using **6** as the starting porphyrin instead of **4**. Column separation gave compound **9** as the first fraction, then **8**, and finally **7**. Recrystallization from DCM/hexane and solvent removal under vacuum gave 27% of oxacalix[6]arene **8** and 15% of oxacalix[8]arene **9**, as well as 45% of oxacalix[4]arene **7. Oxacalix[4]arene 7:** HRMALDI-TOF Calcd. for $C_{100}H_{57}N_{12}O_{12}$ 1628.4250, found m/z 1618.4295. UV-vis (DCM): λ_{max} (log ε) 450 (5.2), 471 (5.2), 623 (4.0) 645 (4.0), 713 (3.7), 763 (3.7) nm. **Oxacalix[6]arene 8:** HRMALDI-TOF Calcd. for $C_{150}H_{84}N_{18}O_{18}$ 2425.6242, found m/z 2425.6414. UV-vis (DCM): λ_{max} (log ε) 414 (5.2), 452 (5.4), 482 (5.4), 630 (4.2), 643 (4.2), 768 (3.8) nm. **Oxacalix[8]arene 9:** HRMALDI-TOF Calcd. for $C_{200}H_{112}N_{24}O_{24}$ 3234.8344, found m/z 3234.8448. UV-vis (DCM): λ_{max} (log ε) 489 (5.5), 638 (4.3), 770 (3.9) nm.

Corrole 11: Compound **10** (264 mg, 1 mmol) and 3,5-dimethoxybenzaldehyde (83 mg, 0.5 mmol) were dissolved in 30 mL DCM. The mixture was purged with nitrogen for 15 min. Then 3 μl TFA in 1 mL DCM was added to the reaction mixture. The mixture was stirred for 5 h and then diluted to 75 mL using DCM. DDQ (227 mg, 1 mmol) was added and the mixture was stirred for 30 min. The solvent was removed and the residue was purified by silica gel column chromatography eluting with 70% DCM/hexane. The violet fraction was collected and dried under vacuum, giving the title compound (168 mg, 51% yield). ^{1}H-NMR (300 MHz $CDCl_3$) 8.00 (2H, brs), 7.39 (2H, brs), 7.21-7.29 (4H, m), 7.07 (4H, s), 6.81 (2H, s) 6.64 (1H, s), 3.86 (6H, s), 2.45 (6H, s), 2.11 (12H, s). MALDI-TOF $[M]^+$ Calcd. for $C_{45}H_{42}N_4O_2$ 670.84, found 670.835.

Corrole **12**: Compound **11** (67 mg, 0.1 mmol), was dissolved in 30 mL DCM. The mixture was purged with nitrogen for 15 min. BBr_3 (150 mg, 6 equiv) in 1 mL DCM was added to the reaction mixture at 0 ℃. The mixture was stirred for 5 h at 0 ℃ and then warmed to room temperature for another 12 h. It was poured into 100 mL water and extracted with DCM. The organic layer was collected and the residue was purified by silica gel column chromatography using 10 % EtOAc/DCM for elution. The greenish major fraction was collected and dried under vacuum, giving the title compound (45 mg, 70 % yield). ^{1}H-NMR (300 MHz CD_2Cl_2) 8.87-8.91 (2H, m), 8.43-8.47 (2H, m), 8.39-8.43 (4H, m), 8.31 (4H, s), 7.34 (1H, s), 6.73 (2H, s), 6.01 (2H, s), 2.71 (3H, s), 2.60 (3H, s), 2.37 (3H, s), 1.91 (6H, s), 1.74 (3H, s). MALDI-TOF $[M]^+$ Calcd. for $C_{43}H_{38}N_4O_2$ 642.79, found 642.50.

Corrole 12Cu: Corrole **12** (32 mg, 0.05 mmol) was dissolved in 10 mL $CHCl_3$ and 3 mL methanol. Then, excess $Cu(acac)_2$ was added. The mixture turned brown in color quickly and was stirred for 1 h. It was filtered to remove salt and then passed through a pad of silica gel. The

reaction gave a quantitative yield. MALDI-TOF M^+ Calcd. for $C_{43}H_{35}CuN_4O_2$ 703.31, found 703.53.

Corrole 13: Corrole **12Cu** (35 mg, 0.05 mmol), 1,5-difluoro-2,4-dinitrobenzene (10.2 mg, 0.05 mmol) and 25 mg of finely ground anhydrous K_2CO_3 (0.18 mmol) were combined in a 20 mL reaction tube. 10 mL DMSO was added and the reaction mixture was stirred vigorously for 1 h at room temperature under ambient atmosphere. The reaction mixture was then partitioned between EtOAc (50 mL) and brine (50 mL). The resulting mixture was separated and the aqueous layer was extracted until colorless. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by passing through a pad of silica gel using 1:1 DCM/hexane as eluting solvents. The only major fraction was collected, concentrated and recrystallized from DCM/hexane. The brown solid was dried under vacuum, giving the target compound (22.1 mg, 50% yield). MALDI-TOF $[M]^+$ Calcd. for $C_{98}H_{70}Cu_2N_{12}O_{12}$ 1734.77, found 1734.05.

Porphyrin-Corrole 15: Compound **10** (26.4 mg, 0.1 mmol) and porphyrin **14** (55.6 mg, 0.05 mmol) were dissolved in 10 mL DCM. The mixture was purged with nitrogen for 15 min. Then 0.3 μl of TFA in 0.5 mL DCM was added to the reaction mixture. The reaction was stirred for 5 h and then diluted to 15 mL using DCM. DDQ (22.7 mg, 0.1 mmol) was added and the mixture was stirred for 30 min. The solvent was removed and the residue was purified on silica gel using 1:1 DCM/hexane. The violet fraction was collected and dried under vacuum, giving the title compound (26.5 mg, 33 % yield). MALDI-TOF $[M]^+$ Calcd. for $C_{99}H_{68}N_{12}O_{12}$ 1617.67, found 1017.94.

Corrole 17: Compound **10** (528 mg, 2 mmol) and compound **16** (506 mg, 1 mmol) were dissolved in 60 mL of DCM. The mixture was purged with nitrogen for 15 min. Then 6 μl of TFA in 1 mL DCM was added to the reaction mixture. The mixture was stirred for 5 h and then diluted to 150 mL using DCM. DDQ (454 mg, 2 mmol) was added and the mixture was stirred for 30 min. The solvent was removed and the residue was purified on silica gel using 2:1 DCM/hexane. The product was obtained in 15% yield (161 mg). ^{1}H-NMR (250 MHz $CDCl_3$) 8.86-8.89 (2H, m), 8.01 (2H, brs), 7.49 (3H, brs), 7.34 (2H, brs), 7.18-7.19 (1H, m), 7.04 (6H, brs), 2.61 (3H, s), 2.37 (3H, s), 2.03 (6H, s). MALDI-TOF $[M]^+$ Calcd. for $C_{55}H_{37}CuF_2N_8O_{10}$ 1071.47, found 1071.749.

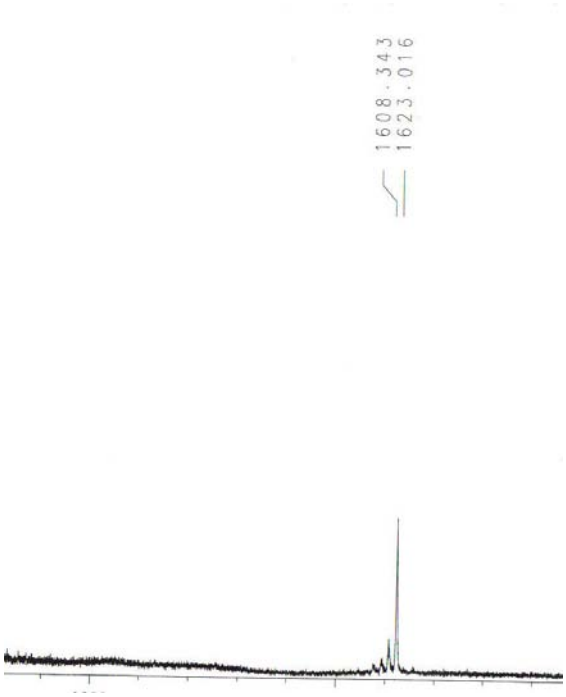
Porphyrin-Corrole 18: Compound **4** (32.2 mg, 0.05 mmol), corrole **17** (53.5 mg, 0.05 mmol) and K_2CO_3 (4 mg) were dissolved in 5 mL DMSO. The mixture was stirred at room temperature for 2 h. It was then poured into 50 mL of water and extracted with EtOAc (50 mL). The organic layer was washed with brine for 3 times. The solvent was removed and the residue was purified on silica gel using 1:2 DCM/hexane. A purple powder (65 mg, 78%) was obtained. MALDI-TOF $[M]^+$ Calcd. for $C_{99}H_{65}CuN_{12}O_{12}$ 1678.19, found 1677.37.

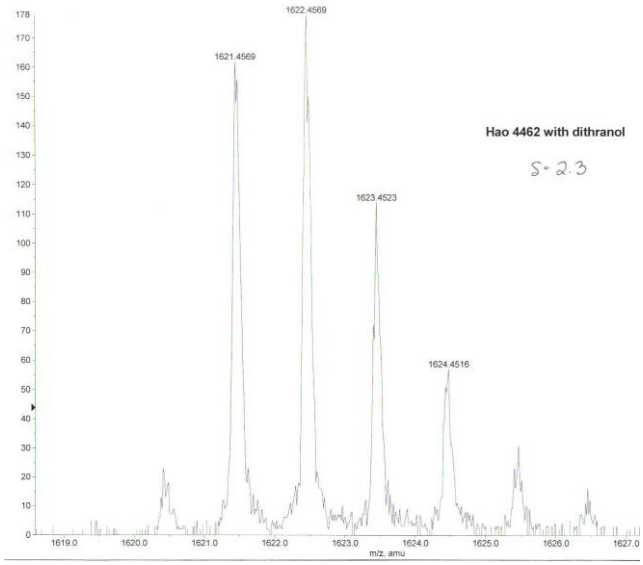
Porphyrin-Corrole 19: 5,15-(3,5-Dihydroxyphenyl)-10,20-(3,5-ditertbutylphenyl)porphyrin ($TPPOH_4$) (22.5 mg, 0.025 mmol), corrole **17** (53.5 mg, 0.05 mmol) and K_2CO_3 (4 mg) were dissolved in 5 mL DMSO. The mixture was stirred at room temperature for 2 h. Then it was poured into 50 mL of water and extracted with EtOAc (50 mL). The organic layer was washed with brine 3 times. The solvent was removed and the residue was purified on silica gel using 1:2 DCM/hexane. A purple powder was obtained (54 mg, 73% yield). MALDI-TOF TOF $[M]^+$ Calcd. for $C_{170}H_{132}Cu_2N_{20}O_{24}$ 2967.1, found 2968.

MALDI-TOF Spectra of Oxacalixarenes:

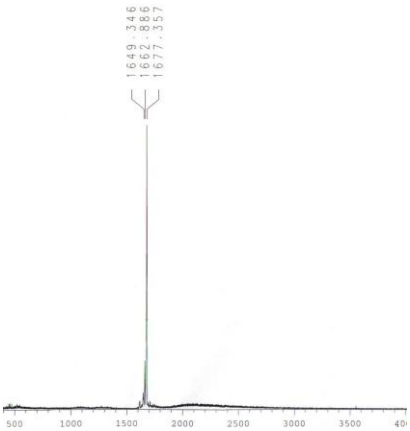
Low resolution MALDI-TOF High resolution MALDI-TOF

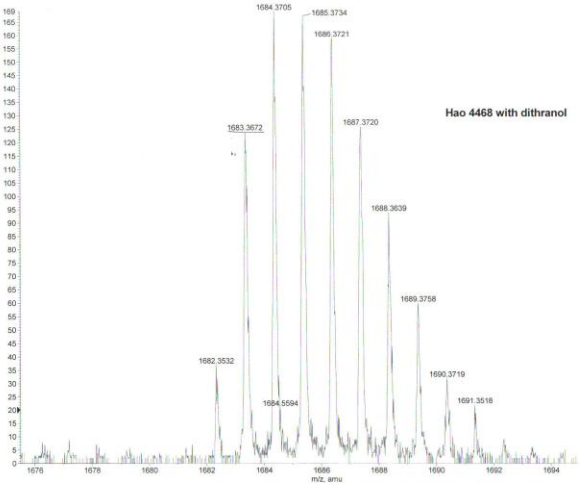
1) Compound **1**



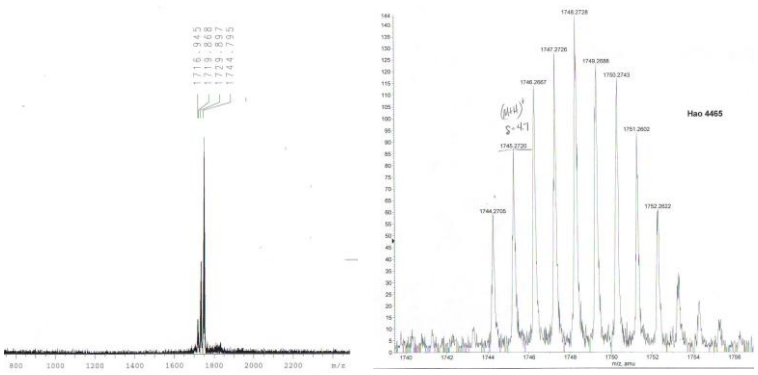


2) Compound **1-H_2Zn**

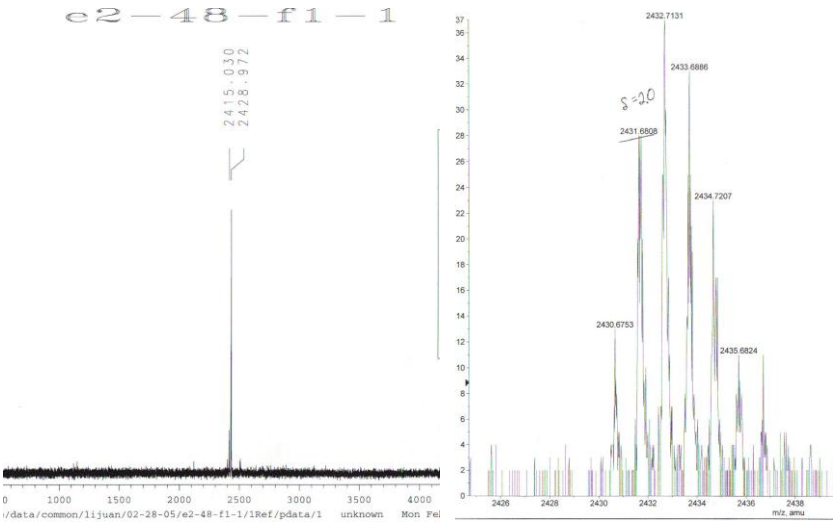




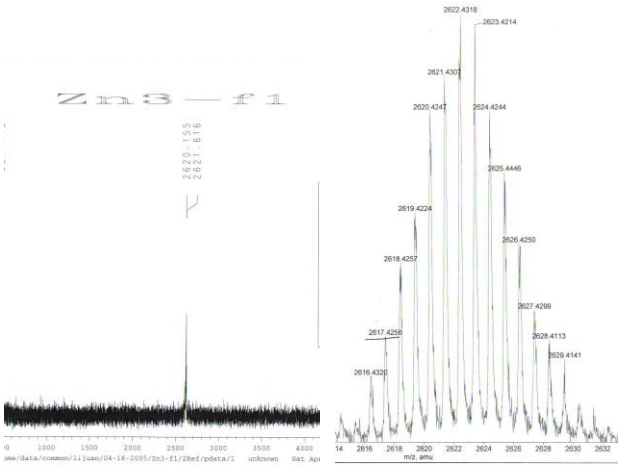
3) Compound **1-Zn_2**



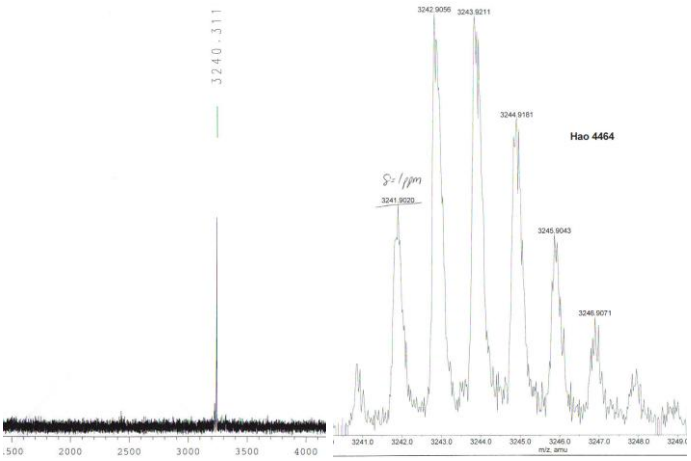
4) Compound **2**



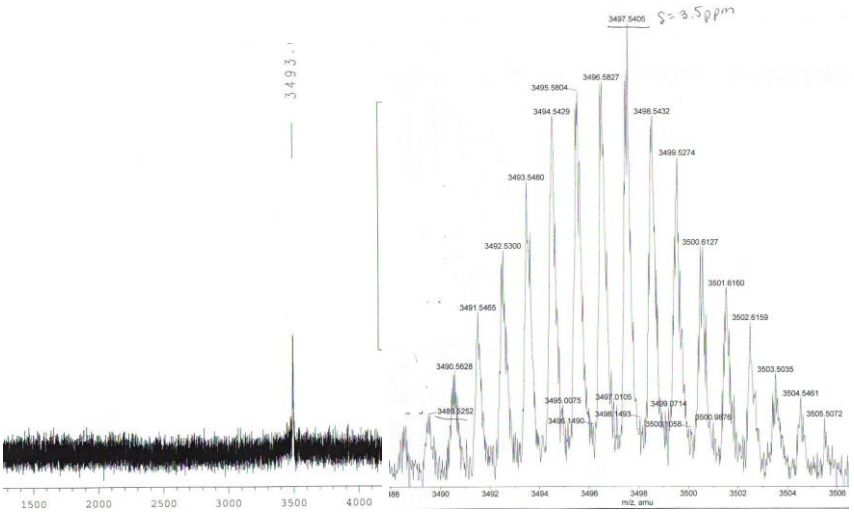
5) Compound **2-Zn$_3$**



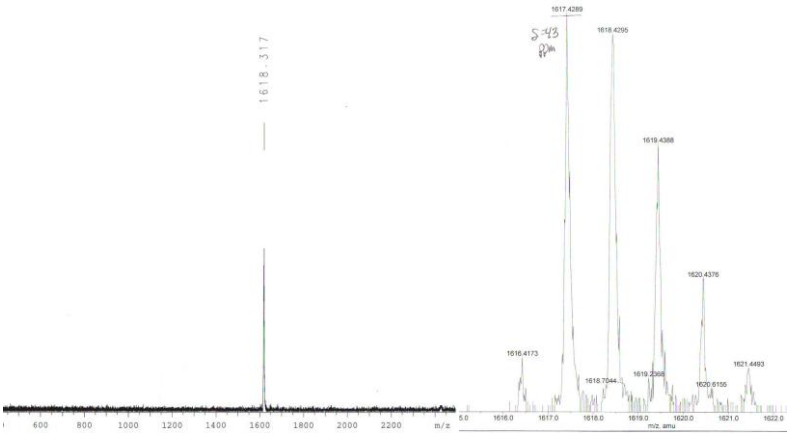
6) Compound **3**



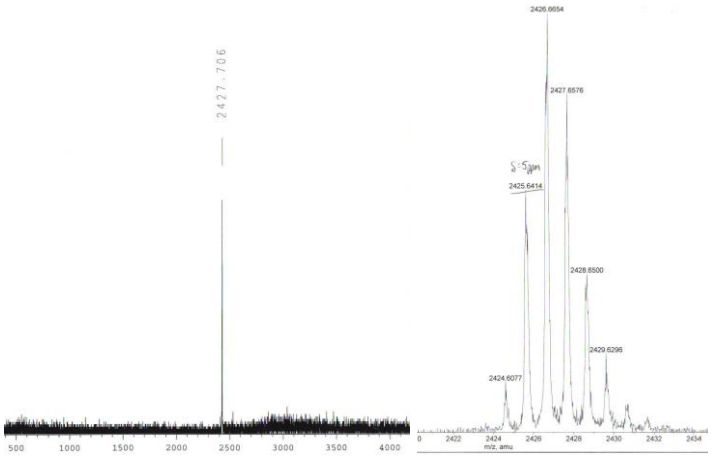
7) Compound **3-Zn_4**



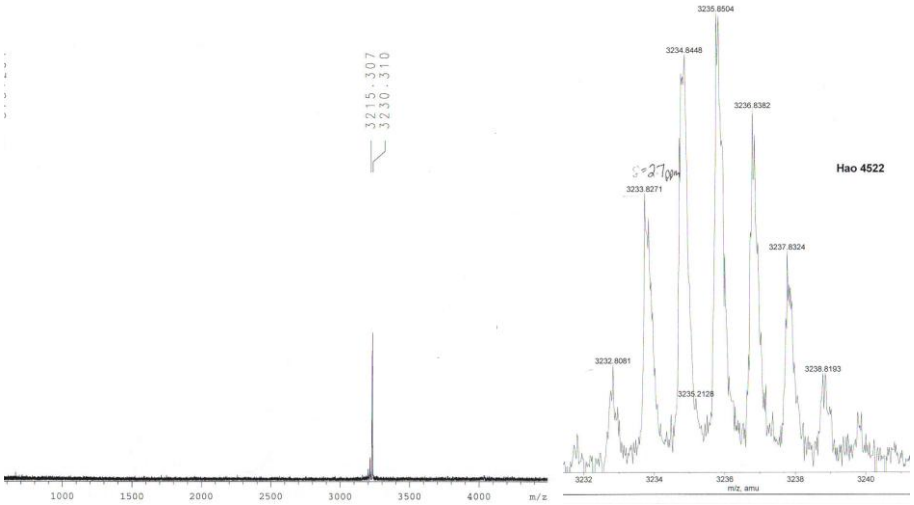
8) Compound **7**



9) Compound **8**



10) Compound **9**



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CHAPTER 6. SYNTHESIS OF PORPHYRIN-SACCHARIDE CONJUGATES VIA CLICK CHEMISTRY

6.1. Introduction

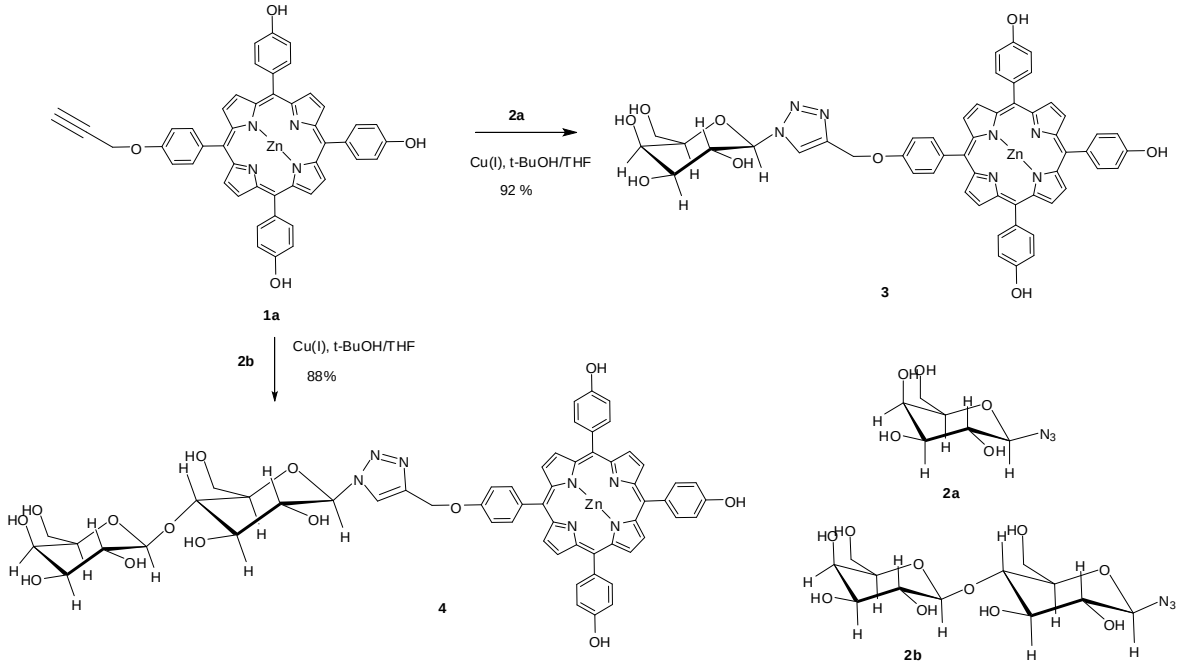
Porphyrin-carbohydrate conjugates have found wide application as photodynamic therapy (PDT) candidates[1]. PDT is a rapidly growing methodology to treat age-related macular degeneration, various skin disorders, and an increasing numbers of cancers that are accessible to irradiation with visible light. It combines a photosensitizer, visible or near infrared light, and oxygen to produce necrosis and/or apoptosis in target tissues. The majority of photosensitizers used for PDT are porphyrin-based compounds. Among these, poor chemical selectivity toward the intended targets is often displayed, and their cellular uptake may arise only from passive, diffusion processes. With the well-established role of carbohydrates in cell recognition, metabolism, and cell labeling, it is known that conjugating carbohydrates to porphyrins can facilitate their passive cellular uptake. In these systems, by modifying the amphiphilicity of porphyrin macrocycles with carbohydrate conjugates, their interaction with the cell surface membranes of tumor cells can be enhanced. For example, Pandey et al. recently demonstrated that a β-galactoside-recognized protein has specificity for galactose- and lactose-benzochlorin conjugates[2].

Meanwhile, the facial approach for functionalization of porphyrin analogs with glycoconjugates remains a challenge. Most of the previous porphyrin-carbohydrate conjugate syntheses are based on the condensation of sugar-containing benzaldehydes[3]. Recently, investigators have taken efforts to avoid total syntheses of porphyrins by introducing carbohydrates after the porphyrin ring formation[4]. Most of the carbohydrates have been conjugated to the phenyl rings of tetraarylporphyrins through an oxygen linkage. Meanwhile, hydrolysis of sugars from these O-glycosides, both *in vivo* and throughout the

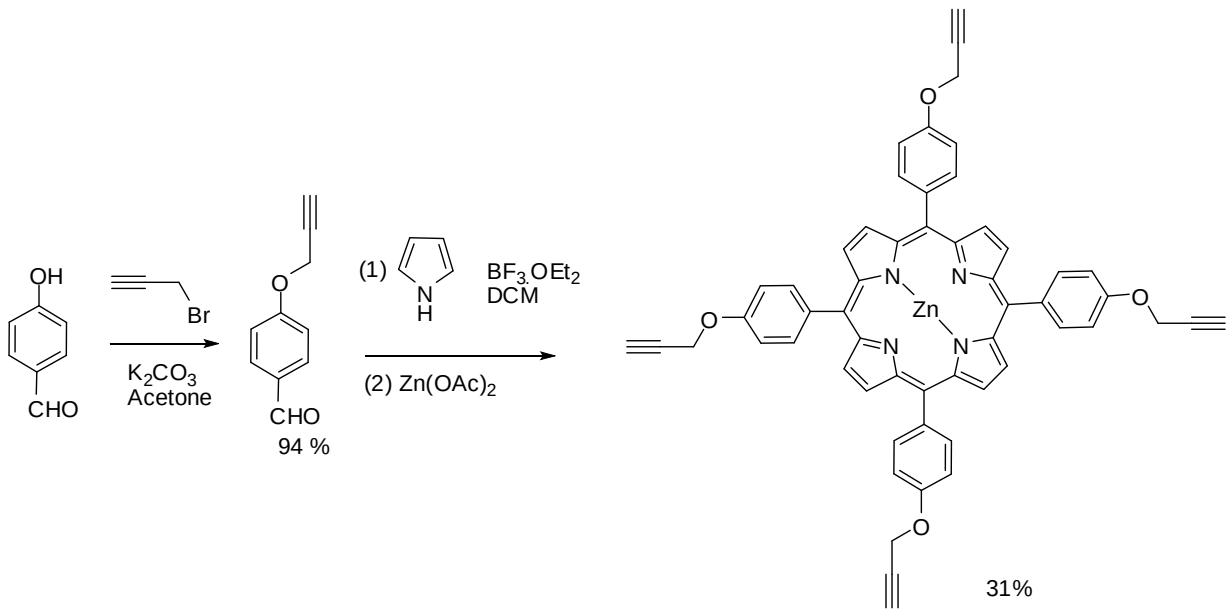
synthesis/purification processes, remains problematic. Approaches to obtain stable glycosides often involve the synthesis of C-linked glycosides. The majority of syntheses of C-linked glycol-porphyrin is complex and often features low yields[5].

When searching for an efficient, high-yielding synthesis of porphyrin-carbohydrate conjugates, "click chemistry" from readily available carbohydrate azides is very attractive. As a prototype of "click chemistry"[6,7], Cu(I) catalyzed 1,3-dipolar cycloaddition of azides to alkynes provides superior regioselectivity and high tolerance of functionalities. Since its first discovery, this reaction has found wide applications in chemistry, biology, and material science. Herein, by adopting "click chemistry", we developed a facial methodology to conjugate carbohydrates to porphyrins. Thus a series of triazole-linked porphyrin-carbohydrate conjugates have been efficiently synthesized.

6.2. Results and Discussion



Scheme 6-1: Synthesis of compounds **3** and **4**.



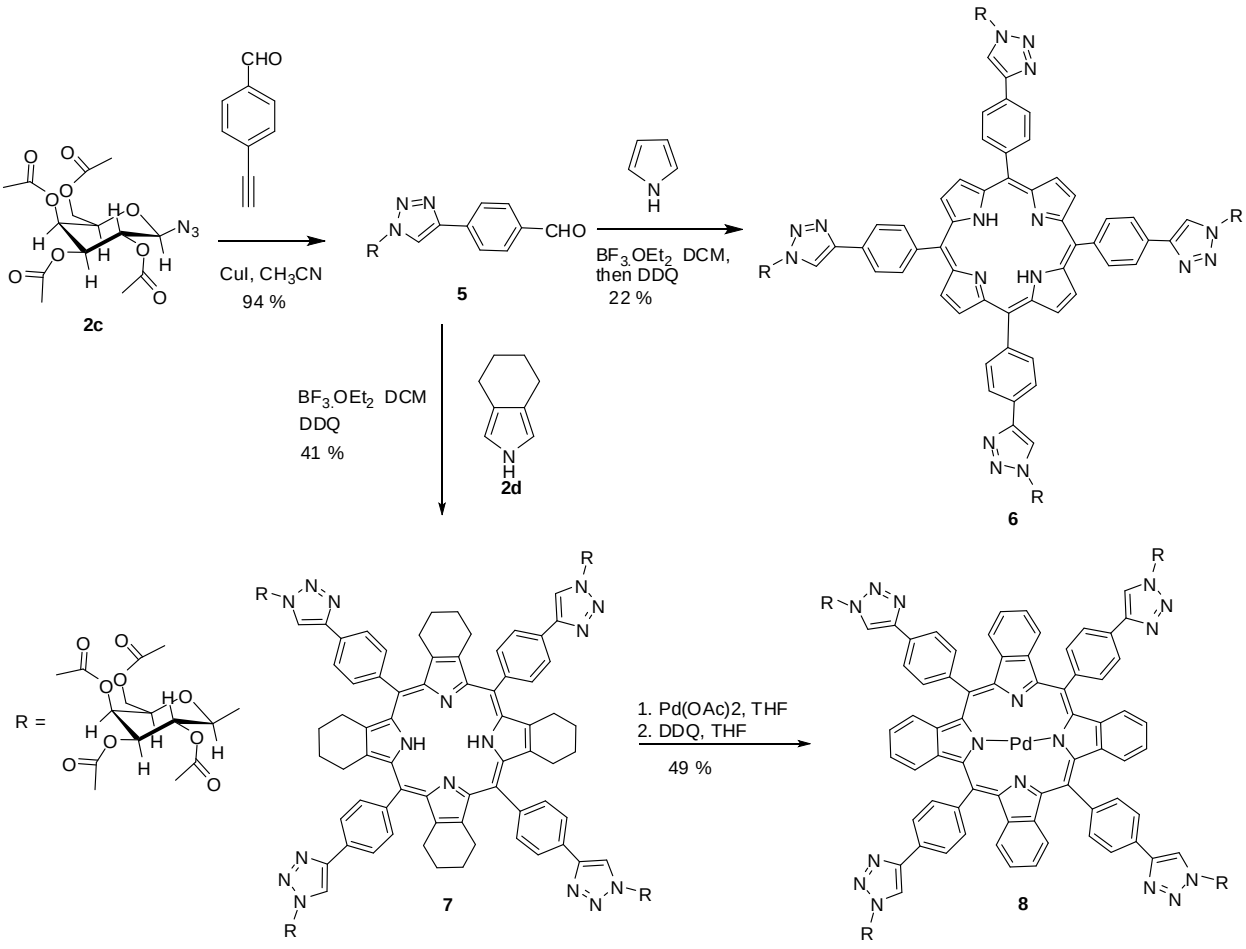
1b

Scheme 6-2: Synthesis of compound **1b**.

Our first synthesis to unsymmetrical conjugates started from compound **1**, which was prepared by mono-alkylation of tetrahydroxyphenylporphyrin followed by zinc insertion. Typical click chemistry conditions developed by Sharpless[7] (t-BuOH: H_2O = 1 : 1, $CuSO_4$ and sodium ascorbate) were applied to conjugate **1a** with the galactose **2a** containing an azide group. The reaction was performed at 70 ℃ in an oil bath and gave compound **3** in 92% yield (*Scheme 6.1*). Interestingly, the corresponding free base **1** failed to re4act under these conditions. Also, possible copper insertion into the porphyrin macrocyle was assumed to be the reason for this failure reaction under the reaction conditions. Thus, the zinc insertion was a good choice since it introduced enhanced reactivity and also avoided copper insertion. Lower temperatures gave incomplete reaction. In a similar way, compound **4** was also synthesized in 88% yield using a lactose-containing azide reagent. It is worth mentioning that unprotected carbohydrate is able to survive these conditions. MALDI-TOF mass spectroscopy gave peaks at 1006.2195 for porphyrin **3** (Calcd. 1006.2155) and 1168.2697 for porphyrin **4** (Calcd. 1168.2683), confirming

the formation of these two compounds. ^{1}H-NMR spectra also matched those expected for the target compounds. The NMR signals were broad due to the possible aggregation of porphyrins.

Next, to achieve the syntheses of tetra-substituted conjugates, the click chemistry method was extended to the conjugation of tetra-carbohydrates to compound **1b,** which was synthesized using Lindsey conditions followed by zinc insertion, as shown in *Scheme 6-2*. However, according to TLC and MALDI mass spectroscopy, the conjugation of **2a** to **1b** always gave a mixture of product. Although different catalysts were tried still it failed to go to completion to generate the desired tetra-carbohydrate-porphyrin conjugate. Protected galactose **2c** was also used in reactions with **1b**, and still the mixture products were obtained.



Scheme 6-3: Syntheses of compounds **6** and **8**.

An alternative synthetic route was employed for the synthesis of tetra-carbohydrate-porphyrin conjugate via a condensation reaction. The galactose-containing benzaldehyde **5** was synthesized in 93.4% yield by reacting **2c** with alkyl-containing benzaldehyde in CH_3CN at room temperature, overnight, with CuI as catalyst and DIPEA as base (*Scheme 6-3*). Using typical click chemistry conditions (t-BuOH/H_2O = 1/1, $CuSO_4$ and sodium ascorbate) at 60 ℃ in an oil bath for two days, only 72.6% yield of the desired product was obtained. The desired tetra-carbohydrate-porphyrin conjugate **6** was synthesized from the condensation of **5** with pyrrole under Lindsey conditions and a 22% yield was obtained. MALDI-TOF mass spectrometry gave a peak at 2203.8, corresponding to the formation of **6**. ^{1}H-NMR and ^{13}C-NMR spectra showed symmetry in the resulting conjugates, and the carbohydrate region of **6** gave a similar spectrum to that of benzaldehyde **5**. The ^{13}C-NMR spectra of the benzaldehyde **5** and conjugate **6** are shown in *Figure 6-1*. Both **5** and **6** gave 6 carbon signals between 60-90 ppm corresponding to the sugar skeletons. In a similar way, porphyrin **7** was synthesized from the condensation of **5** with pyrrole **2d** under Lindsey conditions, and a 41% yield was obtained. The desired tetracarbohydrate-benzoporphyrin conjugate **8** was obtained from the insertion of Pd into porphyrin **7** and subsequent oxidation with DDQ in THF; eventually **8** was obtained in 49% yield. The relatively low yield was attributed to the partial removal of the protecting ester group of the sugar with the presence of $Pd(OAc)_2$ and evidence for this conclusion was the generation of polar green spots on TLC. The final step, deprotection of the ester group attached to the carbohydrate group of **6,** was achieved by using 0.5 M methanol/sodium methoxide, and this was followed by insertion of zinc by using a literature method[4], from which the target carbohydrate-porphyrin conjugate **9** was obtained in 91% yield. A similar procedure was used for the deprotection of tetra-carbohydrate-benzoporphyrin conjugate **8**, and the desired conjugate **10** was

obtained in 89% yield. These target carbohydrate-porphyrin conjugates are very soluble in most polar organic solvent and even water.

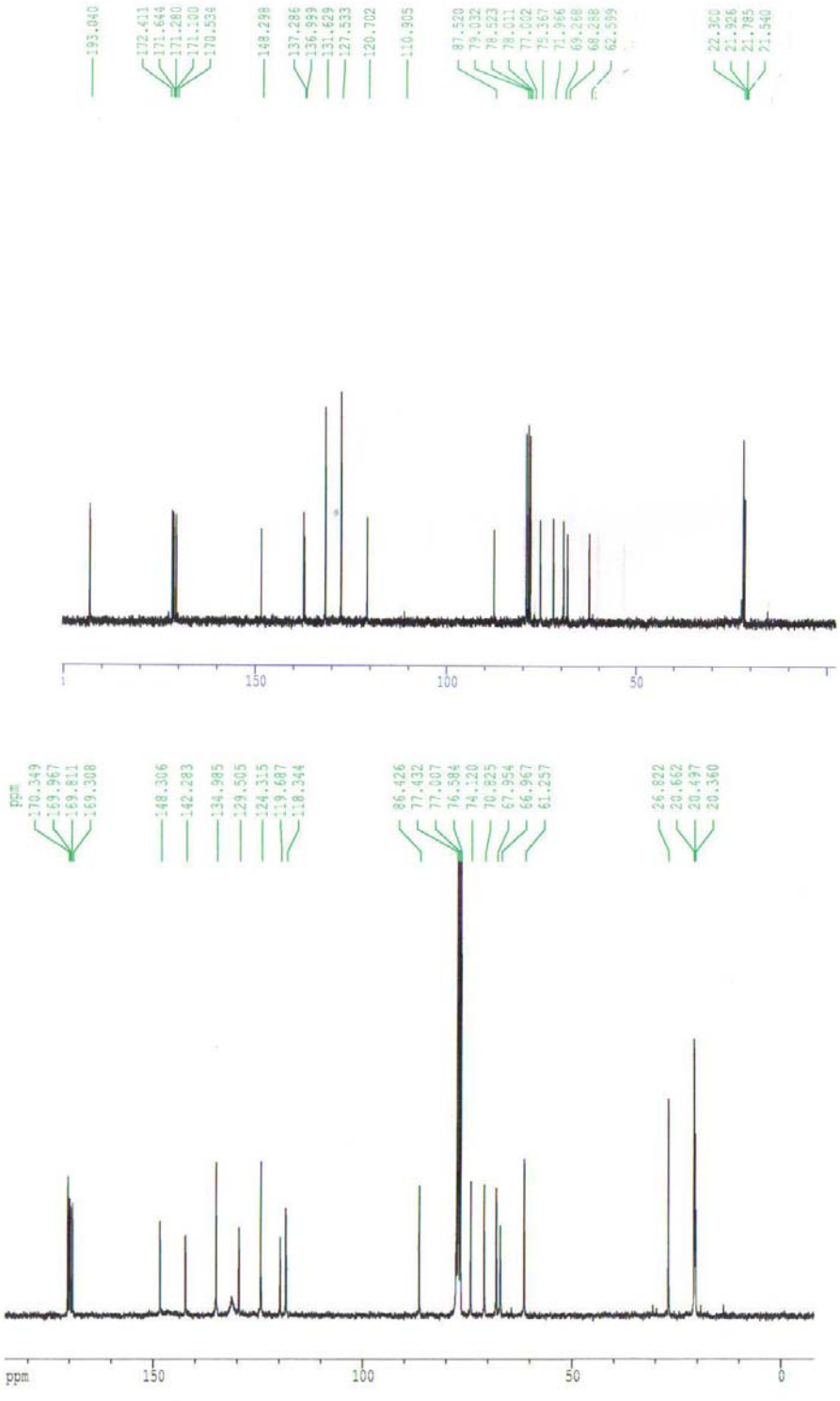
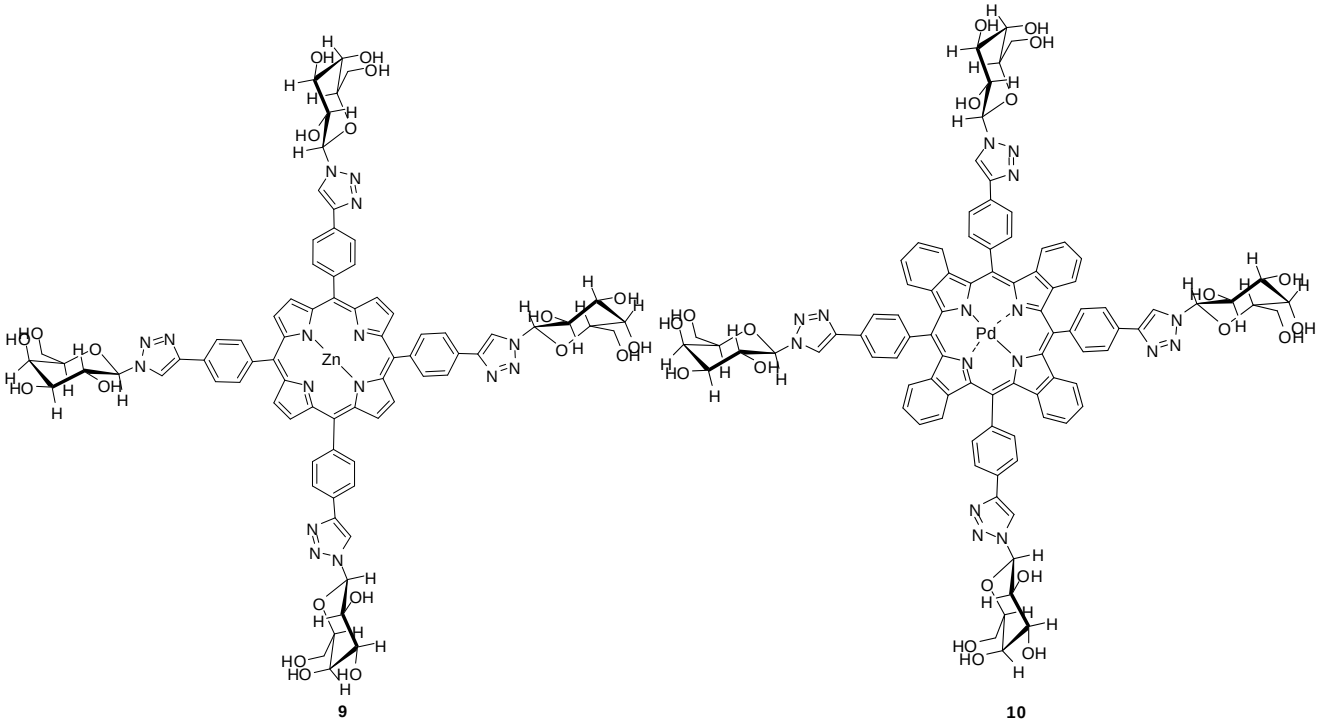


Figure 6-1: ^{13}C-NMR spectra of aldehyde **5** (top) and porphyrin **6** (bottom).

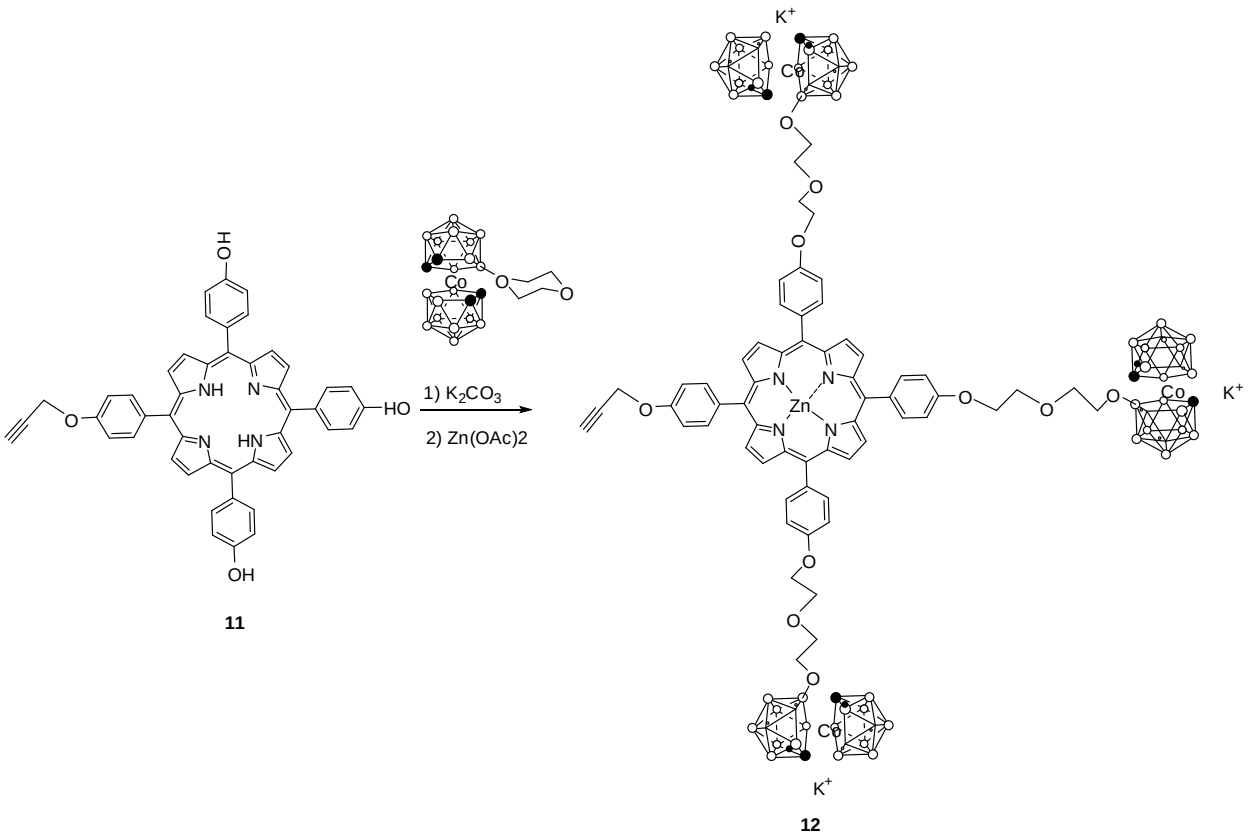
Attracted to the possible high boron content and good water-solubility of the resulting compounds, further modifications of the hydroxyl groups of porphyrin **3** and **4** were attempted using the ring-opening reaction as described in Chapter 2; but it failed to generate the desired products. The reaction did take place but the outcome was more complicated than expected. MALDI-TOF mass spectrometry of the reaction mixture indicated the absence of the target compound. It was surprising to see the failure of this reaction, since the protected carbohydrate-containing analogs of porphyrin **3** and **4** were found to be able to successfully perform and generate the desired product. Meanwhile, porphyrin **12** was also synthesized by using the ring-opening reaction as described in Chapter 2, followed by insertion of zinc, in 87% overall yield (*Scheme 6-4*). Unfortunately, subsequent conjugation of the carbohydrate to **12** using a similar procedure as shown in *Scheme 6-1* failed to generate the desired product; only the starting material was recovered, even using a variety of different reaction conditions.



9 **10**

Figure 6-2: Chemical structures of conjugates **9** and **10.**

In conclusion, both symmetrical and unsymmetrical glycol-porphyrin conjugates were efficiently synthesized using "click chemistry". Because a variety of carbohydrate azides are readily available, this flexible and mild synthetic method will find wide applications for the easy access to carbohydrate-porphyrin conjugates.



Scheme 6-4: Synthesis of porphyrin **12**.

6.3. Experimental

All materials were purchased from Sigma-Aldrich. General experimental conditions are the same as in the previous Chapter 5. Porphyrin **1** was synthesized by mono-alkylation according to the method reported in Chapter 1. Compounds **2a-2c** are commercially available from Aldrich. Compound **2d** was synthesized in two steps according to the literature.

Porphyrin 3: Porphyrin **1a** (18 mg, 0.023 mmol), compound **2a** (6.3 mg, 0.029 mmol), $CuSO_4.5H_2O$ (1.5 mg), and sodium ascorbate (2 mg) were mixed in a 20 mL reaction vial. 10

mL tBuOH: H_2O = 1:1 was added to the reaction mixture and the mixture was stirred at 70 ℃ for 24 h. The reaction was stopped and extracted with EtOAc. The organic layer was dried and passed through a pad of silica gel; a trace amount of the unreacted porphyrin was removed by EtOAc elution, and target compound was eluted using acetone. The target compound was dried under vacuum to give 21.3 mg (92 % yield). ^{1}H-NMR (acetone-d_6, 250 MHz) 8.92 (6H, brs), 8.80 (2H, brs), 8.37 (1H, s), 8.12 (2H, brs), 8.02-8.04 (6H, m), 7.46 (2H, m), 7.28 (6H, m), 7.06 (3H, brs), 5.65 (1H, d, J = 7.66 Hz), 5.40 (2H, s), 4.61 (1H, brs), 4.34 (2H, brs), 4.06 (2H, brs), 3.96 (2H, brs), 3.86 (1H, m), 3.75-3.76 (4H, m). HRMS (ESI-TOF) $[M+Na]^+$ Calcd. for $C_{53}H_{41}N_7NaO_9Zn$ 1006.2155, found 1006.2195.

Porphyrin 4: Porphyrin **1a** (18 mg, 0.023 mmol), compound **2b** (11 mg, 0.03 mmol), $CuSO_4.5H_2O$ (1.5 mg), and sodium ascorbate (2 mg) were mixed in a 20 mL reaction vial. 10 mL tBuOH: H_2O = 1:1 was added to the reaction mixture and the reaction was stirred at 70 ℃ for 24 h. The reaction was stopped and the mixture was extracted with EtOAc. The organic layer was dried and passed through a pad of silica gel; a trace amount of the unreacted porphyrin was removed by EtOAc and target was eluted with acetone. The product was dried under vacuum to give the title compound (23.6 mg) in 88 % yield. ^{1}H-NMR (acetone-d_6, 250 MHz) 8.78 (8H, brs), 8.35 (1H, brs), 7.91-7.99 (8H, m), 7.09-7.26 (8H, m), 6.91 (3H, brs), 5.64 (1H, brs), 5.35 (2H, brs), 4.61 (1H, brs), 4.34 (2H, brs), 3.44-3.99 (17H, m). HRMS (ESI-TOF) $[M+Na]^+$ Calcd. for $C_{59}H_{51}N_7NaO_{14}Zn$ 1168.2683, found 1168.2697. MALDI-TOF $[M+H]^+$ Calcd. for $C_{59}H_{52}N_7O_{14}Zn$ 1168.2683, found 1168.2697.

Aldehyde 5: 4-Ethynylbenzaldehyde (260 mg, 2 mmol), sugar azide (700 mg, 1.86 mmol) and CuI (38.2 mg, 0.2 mmol) were added to 20 mL of CH_3CN. Then 0.9 mL DIPEA was added and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated and

partitioned between DCM and water. The organic layer was evaporated and the residue was purified on silica gel using 50% EtOAc in DCM. The reaction gave 883 mg of the title compound (93.4% yield). ^{1}H-NMR ($CDCl_3$, 250 MHz) 9.88 (1H, s), 8.12 (1H, s), 7.89 (2H, d, J = 8.26 Hz), 7.79 (2H, d, J = 8.38 Hz), 5.86 (1H, d, J = 9.26 Hz), 5.46-5.54 (2H, m), 5.21 (1H, dd, J = 10.24, 3.32 Hz), 4.22-4.25 (1H, m), 4.06-4.09 (2H, m), 2.11 (3H, s), 1.90 (3H, s), 1.89 (3H, s), 1.77 (3H, s); ^{13}C-NMR ($CDCl_3$, 62.9 MHz) 193.0,172.4, 171.6, 171.2, 171.1, 148.3, 137.3, 137.0, 131.6, 127.5, 120.7, 87.5, 75.4, 71.9, 69.3, 68.3, 62.6, 22.3, 21.9, 21.8, 21.5. MALDI-TOF $[M+H]^+$ Calcd. for $C_{23}H_{26}N_3O_{10}$ 504.47, found 504.665.

Porphyrin 6: Compound **5** (252.3 mg, 0.5 mmol) and pyrrole 35 μL were dissolved in 50 mL of dry DCM. The mixture was stirred under argon for 15 min, and then 20 μL $BF_3.OEt_2$ solution (2.5 M in DCM) was added to the reaction mixture. The reaction was stirred at room temperature for 1 h. DDQ (227 mg, 1 mmol) was added and the mixture was stirred for another 1 h. The reaction mixture was evaporated and separated on a silica gel column using first DCM to elute some less polar byproduct and with EtOAc to elute the target molecule. The product was dried and obtained (58 mg) as a purple solid in 21% yield. ^{1}H-NMR ($CDCl_3$, 250 MHz) 8.95 (8H, s), 8.36 (4H, s), 8.26-8.34 (16H, m), 6.04 (4H, d, J = 9.29 Hz), 5.73-5.81 (4H, t, J = 9.63 Hz), 5.65-5.66 (4H, m), 5.36-5.41 (4H, m), 4.35-4.40 (4H, m), 4.27-4.29 (8H, m), 2.30 (12H, s), 2.11 (12H, s), 2.08 (12H, s), 2.04 (12H, s); ^{13}C-NMR ($CDCl_3$, 62.9 MHz) 170.3, 170.0, 169.8, 169.3, 148.3, 142.3, 135.0, 129.5, 124.3.5, 119.7, 118.3, 86.4, 74.1, 70.8, 67.9, 67.0, 61.3, 26.8, 20.7, 20.5, 20.3. MALDI-TOF M^+ Calcd. for $C_{108}H_{106}N_{16}O_{36}$ 2204.08, found 2203.806.

Porphyrin 7: Compound **5** (504 mg, 1 mmol) and pyrrole **2d** (125 mg, 1 mmol) were dissolved in 100 mL of dry DCM. The mixture was stirred under argon for 15 min, and then 60 μL $BF_3.OEt_2$ solution (2.5 M in DCM) was added. The reaction mixture was stirred at room

temperature for 5 h without light. DDQ (300 mg, 1.32 mmol) was added and the mixture was stirred overnight. The reaction mixture was evaporated and separated on a silica gel column using first DCM to elute some less polar byproduct, and using EtOAc to elute the product. The product was dried isolated (248 mg) as a green solid in 41 % yield. ^{1}H-NMR ($CDCl_3$, 250 MHz) 9.02 (4H, s), 8.29 (8H, d, J = 7.48 Hz), 8.20 (8H, d, J = 7.99 Hz), 6.00 (4H, d, J = 9.48 Hz), 5.74-5.82 (4H, t, J = 9.73 Hz), 5.59-5.63 (4H, m), 5.32-5.37 (4H, m), 4.26-4.33 (12H, m), 2.25-2.36 (16H, t), 2.18 (12H, s), 2.09 (12H, s), 2.03 (24H, s), 1.25 (16H, br). NH was not observed due to protonation. MALDI-TOF $[M+H]^+$ Calcd. for $C_{124}H_{131}N_{16}O_{36}$ 2419.89, found 2419.867.

Porphyrin 8: Porphyrin **7** (61 mg, 0.025 mmol) and $Pd(OAc)_2$ (44 mg, 0.18 mmol) were dissolved in 30 mL HPLC grade CH_3CN. The reaction mixture was stirred at 60 ℃ for 30 min; the solution changed in color to red after a few min. The solvent was evaporated and the residue was partitioned between EtOAc and water. The organic layer was dried, evaporated and the residue was dissolved into 10 mL THF. DDQ (200 mg, 0.8 mmol) was added and the mixture was refluxing for 1.5 h. The color changed from red to green during 15 min, and the reaction progress was monitored by UV-vis. 100 mL EtOAc was added and the mixture was washed with water, 0.1 M HCl, and brine to remove excess DDQ. The organic layer was dried and passed through a silica gel column, collecting the first green band using EtOAc and DCM for elution. The fraction was dried and gave the product as a green solid (25.5 mg) in 4 % yield over the two steps. ^{1}H-NMR (acetone-d_6, 300 MHz) 9.03 (4H, s), 8.55 (8H, d, J = 7.89 Hz), 8.37 (8H, d, J = 7.73 Hz), 7.32 (8H, brs), 7.32 (8H, brs), 6.42 (4H, d, J = 9.30 Hz), 5.91 (4H, t, J = 9.69 Hz), 5.65 (4H, d, J = 2.44 Hz), 5.56 (4H, dd, J = 10.24, 3.34 Hz), 4.73-4.77 (4H, m), 4.21-4.36 (8H, m), 2.26 (12H, s), 2.09 (12H, s), 2.06 (12H, s), 2.01 (12H, s); MALDI-TOF $[M+H]^+$ Calcd. for $C_{124}H_{123}N_{16}O_{36}Pd$ 2507.65, found 2507.672.

Compound 9: Compound **7** (44.1 mg, 0.02 mmol) was dissolved in 20 mL of methanol. 100 μL of NaOMe solution (0.5 M in methanol) was added. The mixture was stirred at room temperature for 1 h. After solvent reduction under vacuum, the crude product was purified by gel filtration on a Sephadex LH20 column eluted with methanol. The pure product was crystallized from methanol/water to give 29.1 mg (91% yield). ^{1}H-NMR (pyridine-d_5, 250 MHz) 9.31 (8H, s), 9.13 (4H, s), 8.43-8.52 (16H, m), 6.50 (4H, d, J = 9.07), 4.50-5.39 (24H, m). MALDI-TOF $[M+H]^+$ Calcd. for $C_{76}H_{73}N_{16}O_{20}Zn$ 1595.90, found 1596.14.

Compound 10: Compound **8** (18.5 mg, 0.007 mmol) was dissolved in 10 mL methanol. 20 μL of NaOMe solution (0.5 M in methanol) was added. The mixture was stirred at room temperature for 1 h. After solvent reduction under vacuum, the crude product was purified by gel filtration on a Sephadex LH20 column eluted with methanol. The pure product was crystallized from methanol/water (11.3 mg) and obtained in 89% yield. MALDI-TOF $[M+H]^+$ Calcd. for $C_{92}H_{80}N_{16}O_{20}Pd$ 1837.14, found 1836.71.

6.4. References

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APPENDIX: LETTERS OF PERMISSION

From: Erhong Hao [mailto:ehao1@lsu.edu]
Sent: 11 July 2007 17:01
To: Gill Cockhead
Subject: permission

To Whom It May Concern,

My name is Erhong Hao. I'm a graduate student in the Department of Chemistry at Louisiana State University. I'm writing to ask the permission for the use of my contributions to the article published in the RSC journals in my doctoral dissertation. I'm one of the authors of those articles. The articles are:

1. **Hao, E. H**.; Vicente, M. G. H., Expeditious Synthesis of Porphyrin-Cobaltacarborane Conjugates. *Chemical Communications* **2005**, 1306-1308.

2. Jiao, L.; **Hao, E. H.**; Fronczek, F. R.; Vicente, M. G. H.; Smith, K. M. Benzoporphyrins via Olefin Ring-Closure Metathesis Methodology. *Chemical Communications* **2006**, 3900-3902.

3. Hao, E. H.; Fronczek, F. R.; Vicente, M. G. H., Carboranylated Pyrroles and Porphyrins via the Suzuki Cross-Coupling Reaction. *Chemical Communications* **2006**, 4900-4902.

Thank you very much for your consideration of this request.

Sincerely,

Erhong Hao

From: Gill Cockhead <CockheadG@rsc.org>
To: Erhong Hao <ehao1@lsu.edu>
Subject: RE: permission
Date: Thu, 12 Jul 2007 08:00:54 +0100

Dear Erhong Hao

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VITA

Erhong Hao was born on April 10, 1978, in Huaining County, Anhui province, China. He enrolled in Shandong University, Jinan, China, in 1996. From Shandong University, he earned his Bachelor of Science degree in chemistry in June of 2000. For his master degree study in chemistry, he enrolled in University of Science &Technology of China, Hefei, China, where he earned his Master of Science degree in chemistry in June of 2003. In August of 2003, with the financial support from the Department of Chemistry of Louisiana State University (LSU), he came to LSU to begin his doctoral degree study in chemistry and soon joined Professor M. Graça H. Vicente's research group to begin doing his research in porphyrin chemistry.